Studies on New Synthetic Reactions of Aryl Halides with Homoallyl Alcohols or Triazoles under Palladium Catalysis(Dissertation_全文)

AUTHOR(S):

Iwasaki, Masayuki

Studies on New Synthetic Reactions of Aryl Halides with Homoallyl Alcohols or Triazoles under Palladium Catalysis

Masayuki Iwasaki

2010

Studies on New Synthetic Reactions of Aryl Halides with Homoallyl Alcohols or Triazoles under Palladium Catalysis

Masayuki Iwasaki

2010

Contents

Abbreviations

Ac	acetyl
Ar	aryl
b.p.	boiling point
br	broad (spectral)
bs	broad singlet (spectral)
Bu	butyl
Bn	benzyl
c	cyclo
°C	degrees Celsius
calcd	calculated
cat.	catalytic
cm	centimeter(s)
Co.	company
COD (cod)	1,5–cyclooctadiene
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
DBA (dba)	dibenzylideneacetone
DMF	*N*,*N*–dimethylformamide
DMPE (dmpe)	1,2–bis(dimethylphosphino)ethane
DMSO	dimethyl sulfoxide
DPPE (dppe)	1,2–bis(diphenylphosphino)ethane
DPPF (dppf)	1,1'-bis(diphenylphosphino)ferrocene
DPPP (dppp)	1,3–bis(diphenylphosphino)propane
E	*entgegen* (means "opposite")
Ed(s).	editor(s)
EI	electron ionization
equiv (eq)	equivalent(s)
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
Hex	hexyl
HMPT	hexamethylphosphoric triamide
HRMS	high–resolution mass spectrum
Hz	hertz (s^{-1})
i	iso
i.e.	that is
IR	infrared (spectrum)
J	coupling constant (in NMR)
m	multiplet (spectral), meter(s), milli
m	meta
M	molar (1 M = 1 mol dm^{-3})
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole
m.p.	melting point
MS3A	molecular sieve 3A
MW	microwaves
n	normal
NBD (nbd)	norbornadiene
NMR	nuclear magnetic resonance
Np	1–naphthyl
o	ortho
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million (in NMR)
Pr	propyl
q	quartet (spectral)
ref(s).	reference(s)
rt	room temperature (25 ± 3 °C)
s (*sec*)	secondary
s	singlet (spectral)
sept	septet (spectral)
t	triplet (spectral)
t (*tert*)	tertiary
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
THP	2–tetrahydropyranyl
TLC	thin-layer chromatography
tol	tolyl
Ts	*p*–toluenesulfonyl
UV	ultraviolet
vide infra	see below
XPhos	dicyclohexyl[2–(2,4,6–triisopropylphen-yl)phenyl]phosphine
Z	*zusammen* (means "together")

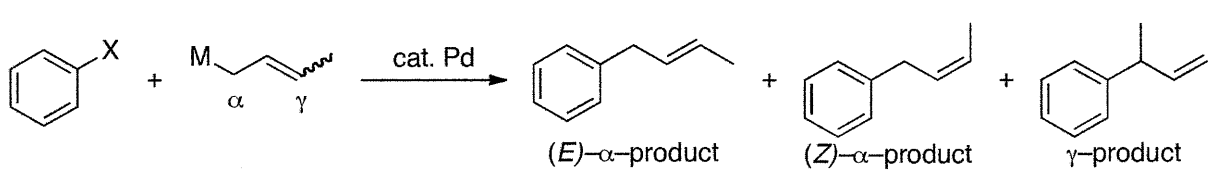
General Introduction

1. Allylation Reaction of Aryl Halides with Allylmetals under Transition Metal Catalysis

Transition–metal–catalyzed cross–coupling reactions rank as one of the most important reactions in organic synthesis and have been extensively investigated.[1] One thus tends to think that the cross–coupling strategy can construct arbitrary carbon–carbon bonds by optimizing reaction conditions. However, despite their seeming simplicity, the cross–coupling reactions of aryl halides with allylmetals represent rare combinations relative to those with arylmetals forming biaryls. In light of the importance of allylation reactions in organic synthesis,[2] further studies on the rare cross–coupling reactions are necessary. However, there are many issues to be resolved, including reaction efficiency and functional group compatibility.

The most critical problem is the regio– and stereoselectivity of the allylation when substituted allylmetals are employed (Scheme 1). For instance, a cross–coupling reaction with a crotyl metal reagent takes place competitively at the α– and γ–positions of the crotyl group. In addition, the product coupled at the α–position usually consists of a mixture of *E* and *Z* isomers. In order that the cross–coupling allylation can become a useful tool for modern organic synthesis, one must establish such regio– and stereochemical control of the allylation. Although some allylation reactions of aryl halides with allylmetals under transition metal catalysis have been reported, their regio– and stereoselectivities of the allylation are not satisfactory, which will be discussed in the following sections.

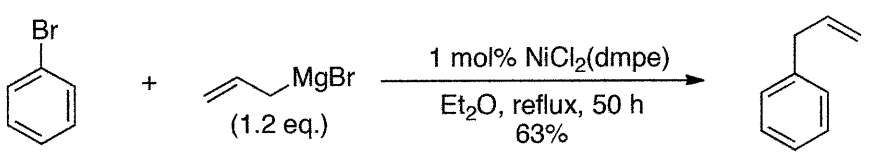
Scheme 1.



1–1. Nickel–Catalyzed Allylation Reaction of Aryl Halides with Allylmagnesiums

Allyl Grignard reagents are useful because they are generally easy to prepare. Kumada and Tamao reported the conventional cross–coupling reaction of aryl bromides with allyl Grignard reagents under nickel catalysis (Scheme 2).[3] Treatment of bromobenzene with allylmagnesium bromide in the presence of a catalytic amount of nickel chloride dmpe complex in ether for 50 h provided the corresponding coupling product. However, the regioselective allylation of aryl halides was not performed. Thus, regioselective and convenient allylation reactions need to be investigated.

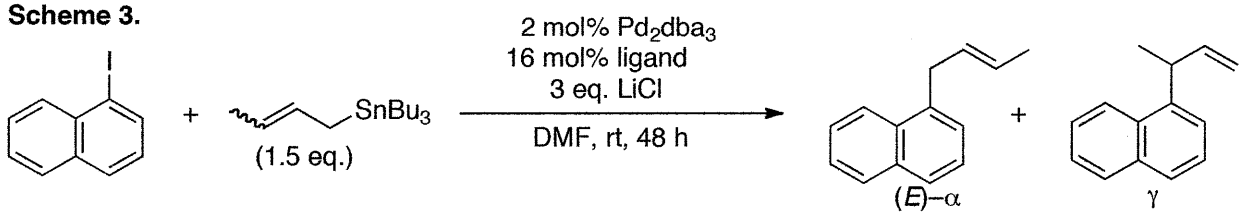
Scheme 2.



1–2. Palladium–Catalyzed Allylation Reaction of Aryl Halides with Allylstannanes

A regiocontrolled coupling reaction of tributylcrotylstannane with 1–iodonaphthalene was reported (Scheme 3).[4a] Use of triphenylarsine as a ligand provided the corresponding (*E*)–α–product selectively, whereas a triphenylphosphine–assisted reaction yielded the γ–product exclusively.[5] Unfortunately, the generality and the efficiency of the reaction are unsatisfactory, and no procedure to obtain (*Z*)–α–product was disclosed. Moreover, organotin compounds have relatively high toxicity, which represents a significant drawback.

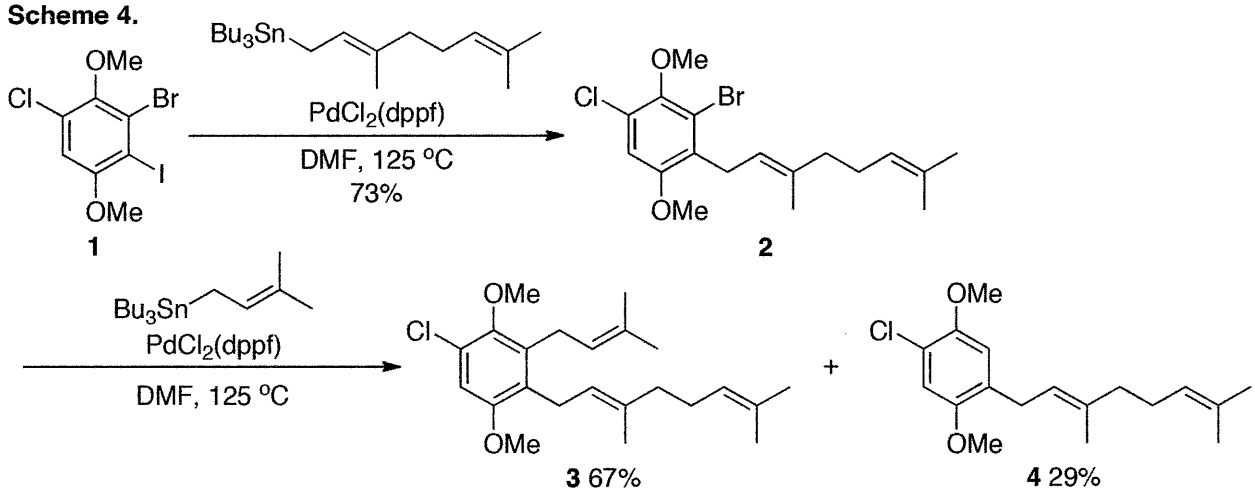
Scheme 3.



entry	ligand	yield	ratio of (*E*)–α : γ
1	$AsPh_3$	61%	91 : 9
2	$P(OCH_2)_3CEt$	14%	79 : 21
3	P(2–furyl)$_3$	71%	15 : 85
4	PPh_3	23%	0 : 100

(±)–A80915G, a member of the napyradiomycin family of antibiotics, has been synthesized by using palladium–catalyzed regioselective allylation reactions of aryl halides with allylstannanes (Scheme 4).[4b] Treatment of trihalogenated compound **1** with tributylgeranyltin under palladium catalysis in DMF at 125 °C for 24 h afforded the desired coupling product **2** exclusively. A small amount of the corresponding hydrodeiodinated compound was observed. Under almost the same reaction conditions, the Stille reaction of **2** afforded product **3** using tributylprenyltin. The major by–product in this case was debrominated compound **4**. Although regioselective allylations of aryl halides were performed in these two reactions, the generality of the regioselective synthesis of allylarenes has not been achieved.

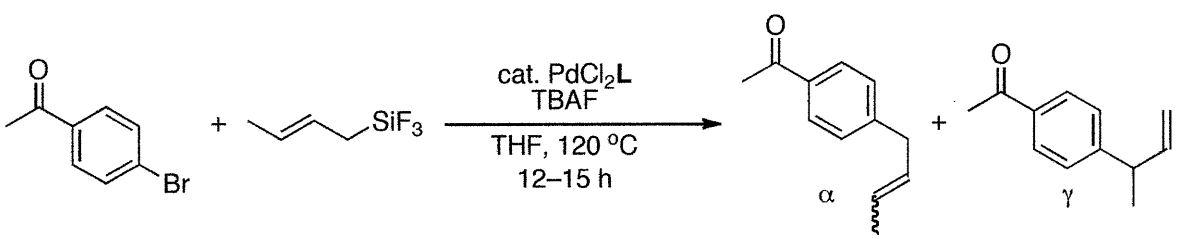
Scheme 4.



1–3. Palladium–Catalyzed Allylation Reaction of Aryl Halides with Allylsilanes

As the pioneering solution to the problem, Hatanaka and Hiyama developed regioselective cross–coupling reactions of aryl halides with substituted allylfluorosilanes (Scheme 5).[6] Monodentate triphenylphosphine led to γ–selectivity,[6a] and bidentate 1,3–bis(diphenylphosphino)propane, to α.[6b] However, the excellent example highlights the difficulty in achieving the cross–coupling allylation from the viewpoint of modern organic synthesis. Specifically, the reactions required heating in sealed tubes and the use of relatively labile allylfluorosilanes and lacked universal stereochemical control of the (*E*)– and (*Z*)–α–products.

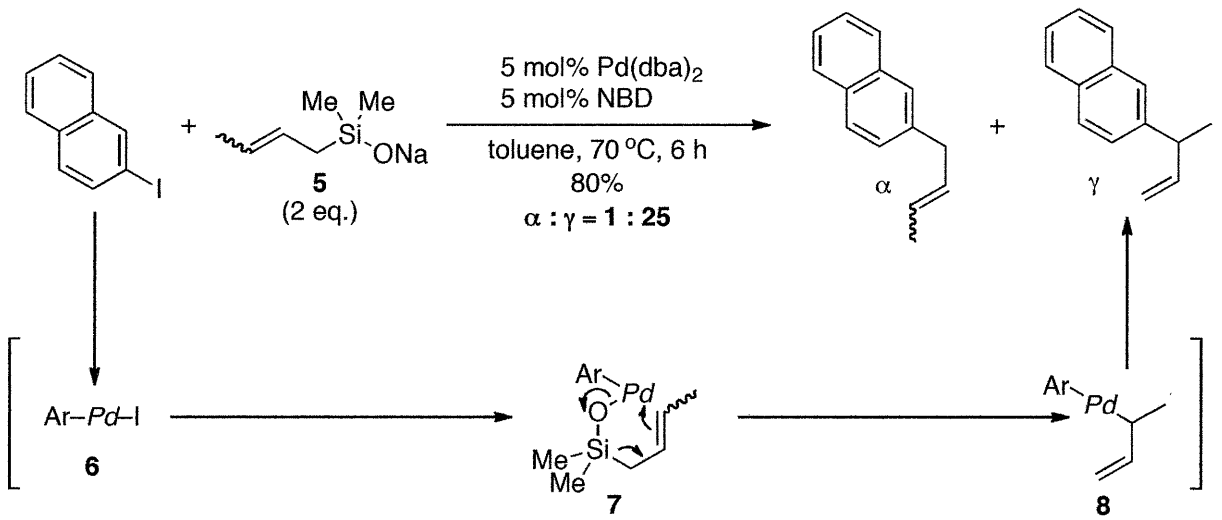
Scheme 5.



entry	L	yield	ratio of α (*E* : *Z*): γ
1	DPPP	92%	99 (7.2 : 1) : 1
2	PPh_3	97%	0 : 100

Recently, Denmark has reported γ–selective allylation of aryl bromides with allylic silanolate salts under palladium catalysis (Scheme 6).[7] The allylation reaction proceeds as follows: (1) after oxidative addition, displacement of the bromide by **5** forms Si–O–Pd linkage, (2) S_E2' transmetalation occurs intramolecularly, and (3) facile reductive elimination of the γ–bound palladium intermediate **8** affords the γ–product with high regioselectivity. Despite the utility of this reaction, the starting allylic silanolate salts require several steps to prepare.

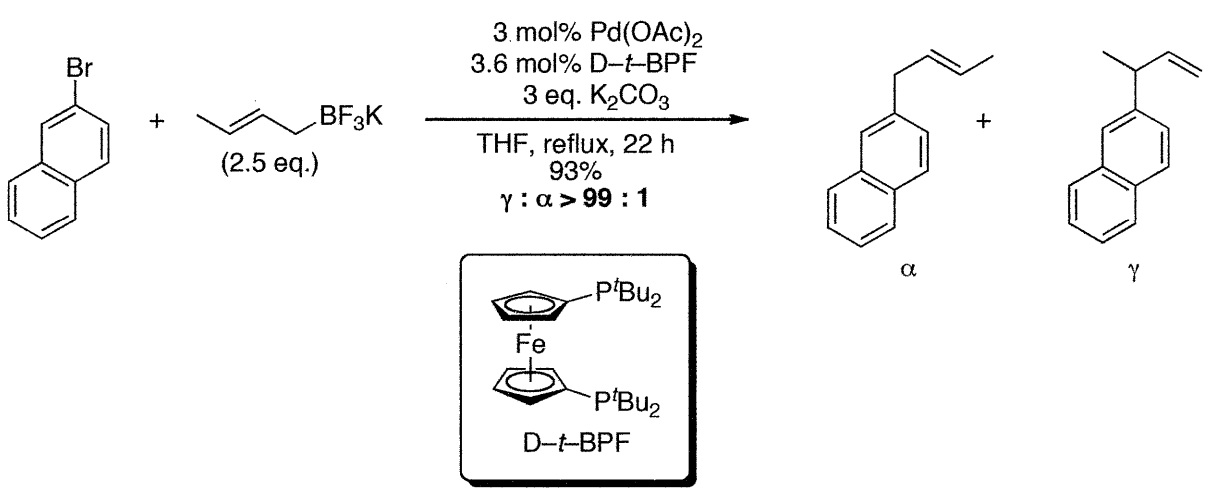
Scheme 6.



1–4. Palladium–Catalyzed Allylation Reaction of Aryl Halides with Allylborons

Recently, a γ–selective cross–coupling reaction with potassium (*E*)–crotyltrifluoroborate was reported, but no α–selectivity was attained (Scheme 7).[8] Enantioselective allylation was also developed by using a chiral diphosphine ligand.

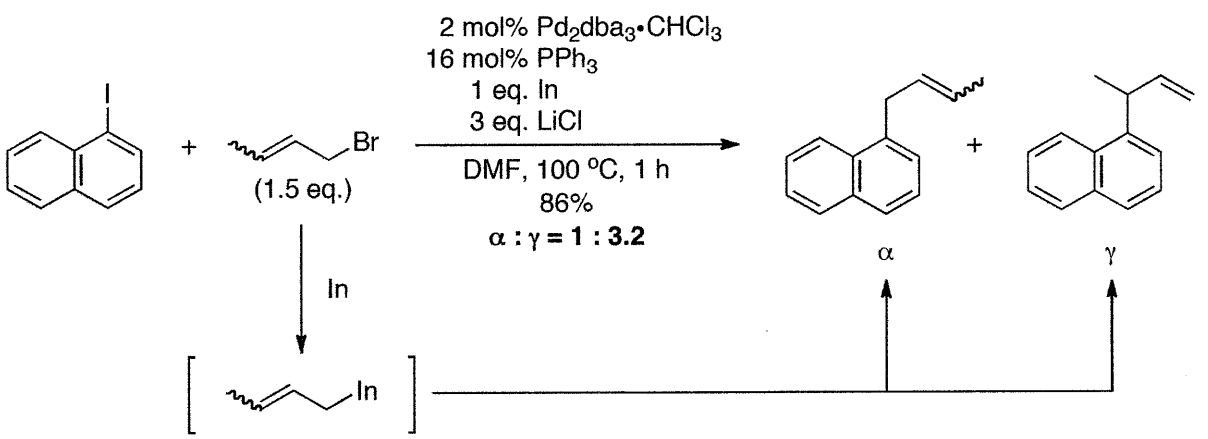
Scheme 7.



1–5. Palladium–Catalyzed Allylation Reaction of Aryl Halides with Allylindiums

Allylindium reagents, generated in situ from the reaction of indium with allyl halides, were effective cross–coupling partners in palladium–catalyzed cross–coupling reactions of aryl halides (Scheme 8).[9] The present method complements the existing synthetic methods thanks to some advantageous properties of allylindium reagents over allylstannanes such as availability, easy handling, high reactivity, operational simplicity, and lower toxicity. However, the regioselectivity is not satisfactory.

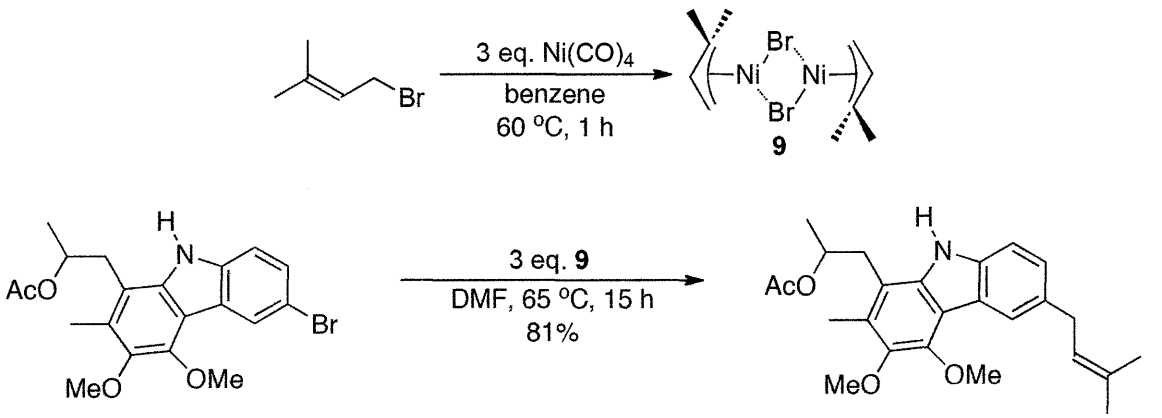
Scheme 8.



1–6. Regioselective Allylation Reaction of Aryl Halides with Stoichiometric Amounts of Allylnickels

According to the report by the Knölker group regarding the synthesis of Carquinostatin **A**, bromo(prenyl)nickel dimer **9** was effective for regioselective prenylation of aryl bromide (Scheme 9).[10] However, the use of a large excess of nickel complex **9** was essential to afford the product with satisfactory efficiency and selectivity. Moreover, a large amount of highly toxic $Ni(CO)_4$ was required for the preparation of **9**, which represents a significant drawback.

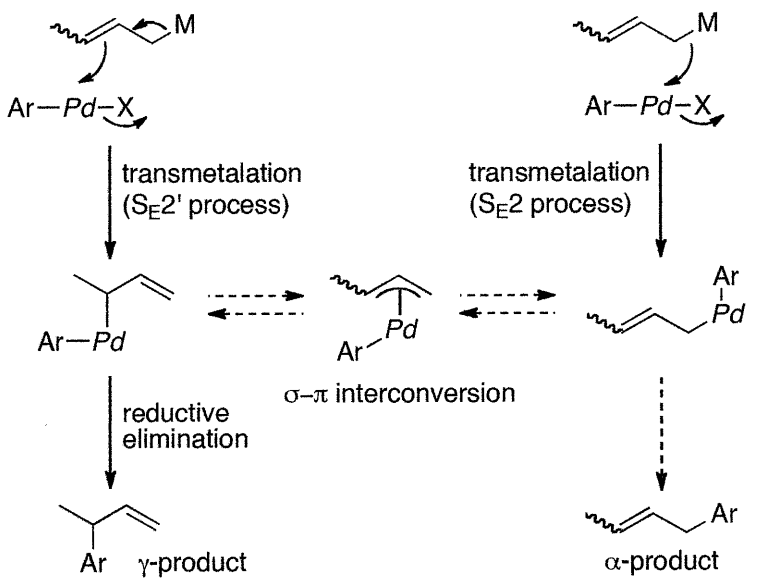
Scheme 9.



1–7. Palladium–Catalyzed Allylation Reaction of Aryl Halides with Homoallyl Alcohols

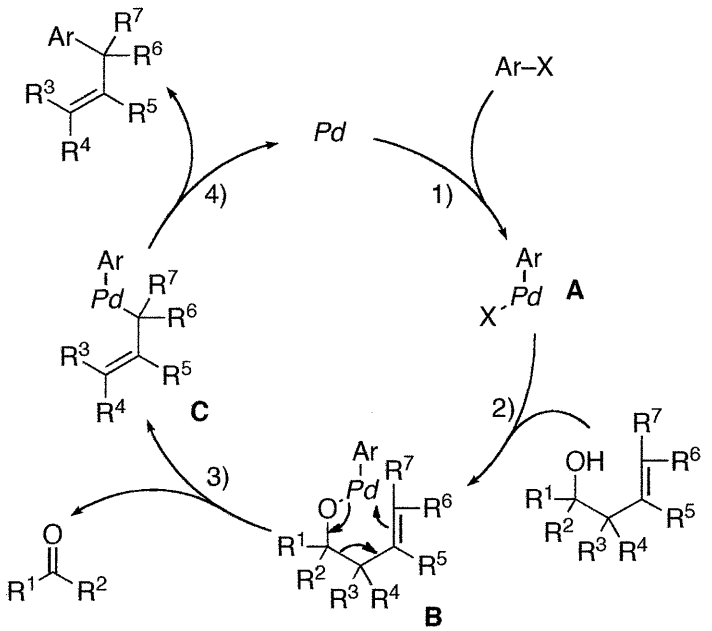
The γ–selectivity observed in the reactions of crotylfluorosilanes and of crotyltrifluoroborate (Section 1–3 and 1–4) was explained by the following hypotheses (Scheme 10):[7,8] (1) the transmetalations between the crotylmetals and arylpalladium halides proceed in an S_E2' process,[11] and (2) aryl(1–methyl–2–propenyl)palladiums, σ–allylpalladiums[12] formed by the transmetalations, predominantly undergo rapid reductive elimination of Pd(0) to afford 1–methyl–2–propenylarenes without suffering from any σ–π interconversion that could lead to the α–product. The hypotheses clearly suggest that one should simply prepare and use the corresponding well–defined allylmetals to obtain the desired products selectively. Nevertheless, preparation of allylmetals having an arbitrary substitution pattern is generally difficult. Moreover, there remains a possibility that the transmetalation would proceed unexpectedly in an S_E2 fashion. Such conduct heavily depends on the structure and electronic factors of the allylmetals used.[11]

Scheme 10.



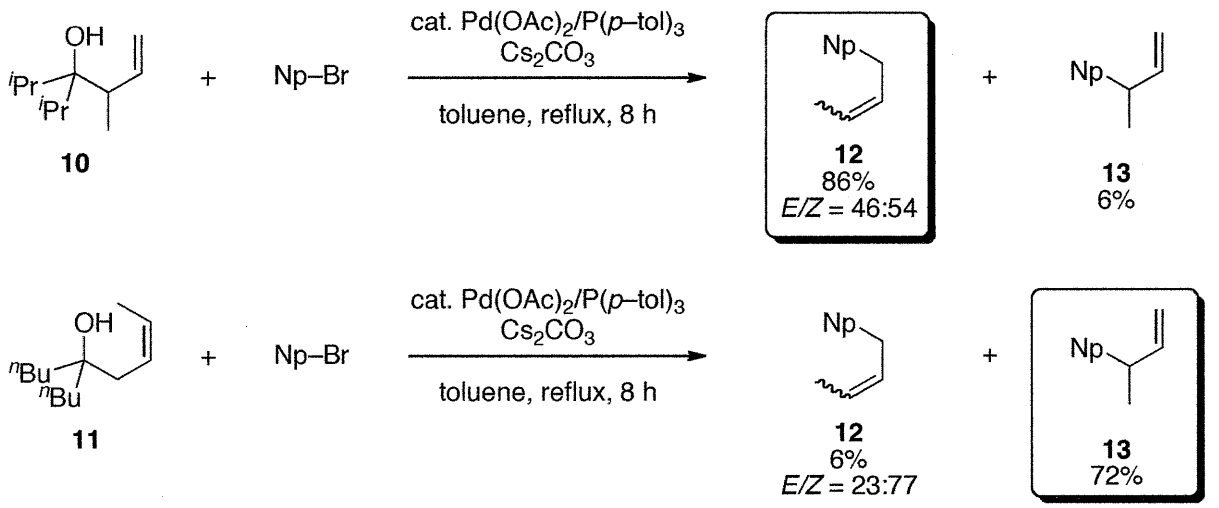
The use of homoallyl alcohols as the allyl sources in the palladium–catalyzed allylations of organic halides instead of allylmetal reagents has been communicated.[13] Scheme 11 illustrates the proposed mechanism. After oxidative addition yielding **A** (step 1), ligand exchange with homoallyl alcohol would take place to afford alkoxy(aryl)palladium **B** (step 2). Retro–allylation reaction of **B**,[14–16] the key step of this strategy, occurred next, providing σ–allyl(aryl)palladium **C** (step 3). Since the retro–allylation proceeds in a concerted fashion via a conformationally regulated six–membered cyclic transition state and since the reductive elimination from **C** (step 4) is faster than the isomerization of **C** to π–allyl(aryl)palladium (see Scheme 10), the stereo– and regiochemical information of the homoallyl alcohol is transferred to **C** and then to the allylated product. In contrast to allylmetals, homoallyl alcohols are not sensitive to air and moisture. Each homoallyl alcohol is available commercially, which would in principle allow for introducing allyl groups of various substitution patterns.

Scheme 11.



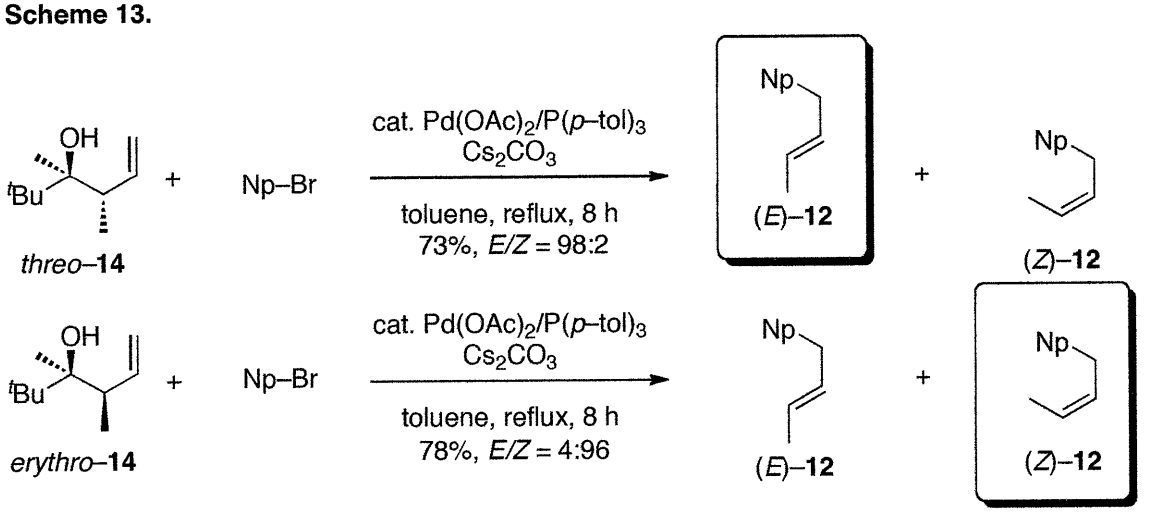
The allylation transfer reaction is highly regiospecific. Treatment of homoallyl alcohol **10** bearing a methyl group at the allylic position with 1–bromonaphthalene in the presence of cesium carbonate under palladium catalysis in boiling toluene provided linear product **12** regioselectively. On the other hand, the reaction of homoallyl alcohol **11** having a methyl group at the olefin terminus gave branched product **13** selectively (Scheme 12).

Scheme 12.



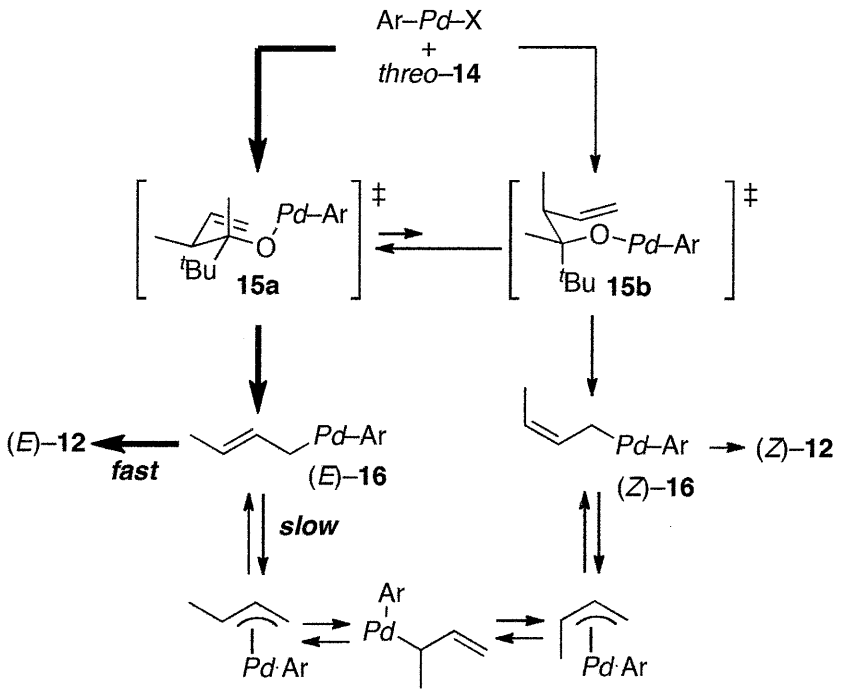
A stereospecific allylation reaction was also available. The reactions of 1–bromonaphthalene with *threo*– and *erythro*–**14**, afforded (*E*)– and (*Z*)–1–crotylnaphthalene, respectively (Scheme 13).

Scheme 13.



The mechanism of the regio– and stereospecific allyl transfer reaction can be rationalized as shown in Scheme 14. Upon the retro–allylation reaction of *threo*–**14**, a chairlike transition state **15a** that locates the *tert*–butyl group at the equatorial position would be most stable among possible transition states, including another chairlike transition state **15b** and twist–boatlike transition states, as determined on the basis of the conventional conformational analysis. Formation of aryl[(*E*)–crotyl]palladium (*E*)–**16** is thus favored. The intermediate probably undergoes reductive elimination so rapidly that its isomerization into π–allylpalladium or any other isomers is negligible. A similar explanation is applicable to the reaction of *erythro*–**14**, where a chairlike transition state having the *tert*–butyl group at the equatorial position and the two methyl groups at the axial positions would be preferred.

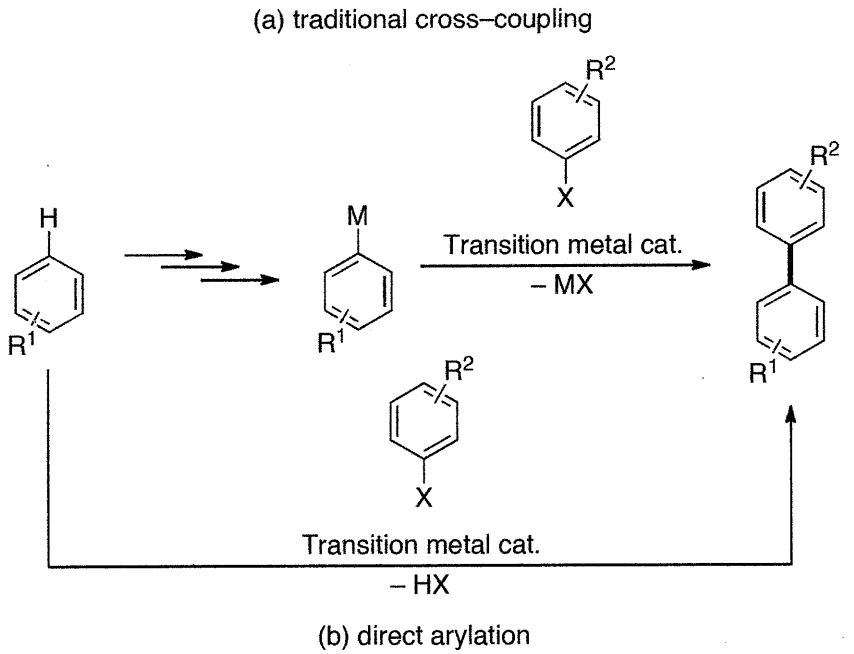
Scheme 14.



2. Direct Arylation Reaction of 1,2,3–Triazoles with Aryl Halides under Transition Metal Catalysis

Biaryls are indispensable structural motifs of various compounds such as natural products, polymers, and molecules with medicinal importance.[17] Their regioselective syntheses are predominantly achieved through transition–metal–catalyzed cross–coupling reactions between organic (pseudo)halides and stoichiometric amounts of organometallic reagents (Scheme15, a), which have matured as reliable tools for the synthesis of biaryls.[1] However, these nucleophilic organometallic reagents are often commercially unavailable or expensive. Their syntheses from the corresponding arenes need many synthetic steps, during which undesired by–products are formed. Therefore, direct arylation reactions through cleavage of C–H bonds represent environmentally and economically benign alternatives (Scheme15, b).[18]

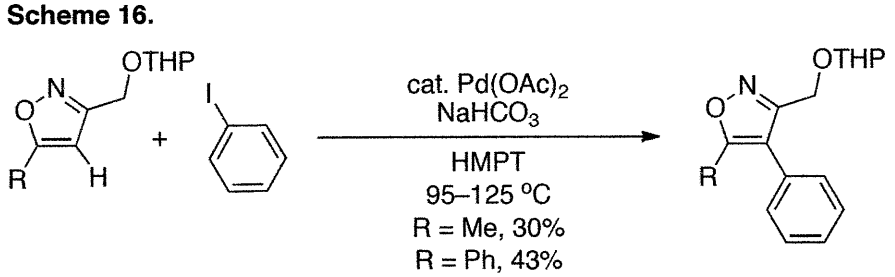
Scheme 15.



Azoles are known to undergo direct intermolecular arylation via C–H bond cleavage on treatment with aryl halides in the presence of suitable catalysts, typically palladium–based ones.[19] Such reactions can be utilized as effective and straightforward methods for making aryl–heteroaryl linkages, which are often found in biologically active compounds and in π–conjugated functional materials.

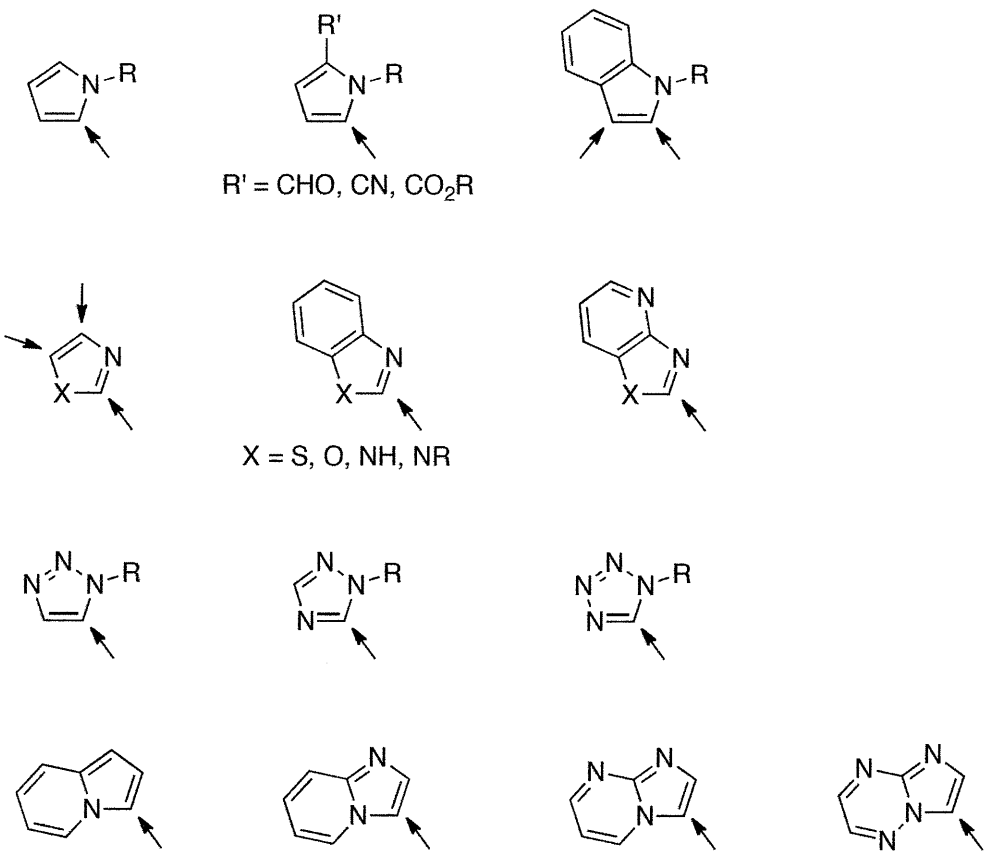
One of the first examples of direct arylation of azoles is the palladium–catalyzed arylation reaction of isoxazoles (Scheme 16).[20] Here, the 3,5–disubstituted substrates undergo phenylation with iodobenzene at the 4–position under palladium catalysis, albeit with moderate efficiency.

Scheme 16.



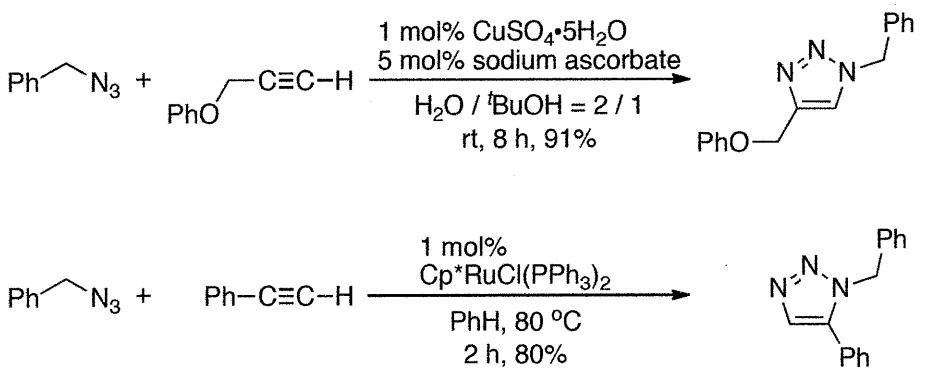
Since the above findings were announced, the direct arylation has been developed significantly.[18] Various kinds of azoles also proved to undergo coupling with aryl halides. Recent representative examples are summarized in Scheme 17. The regioselectivity of intermolecular direct arylation primarily depends on the type of heterocycle.

Scheme 17.



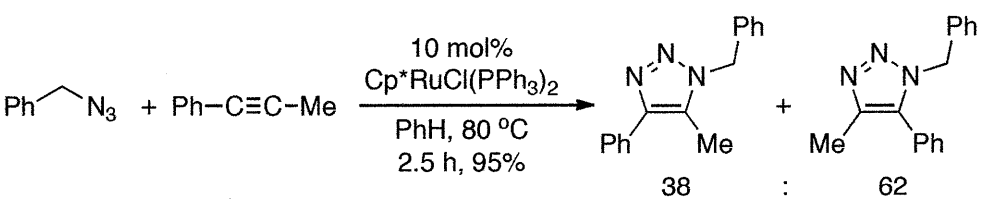
Among azoles, 1,2,3–triazoles are especially important heterocycles in medicinal chemistry. One of the representative methods for the syntheses of 1,2,3–triazoles is the reaction of alkynes with organic azides. Highly regioselective syntheses of 1,4– and 1,5–disubstituted triazoles have been established by using copper[21a] and ruthenium[21b] catalysts, respectively (Scheme 18). The scope of the substrates in these two reactions is so broad that these reactions are quite useful for regioselective syntheses of disubstituted 1,2,3–triazoles.

Scheme 18.



However, transition–metal–catalyzed as well as thermal coupling reactions of internal alkynes with organic azides lack regioselectivity and/or generality. For instance, according to the report by Weinreb, the ruthenium–catalyzed [3+2]cycloaddition reaction of internal alkynes with organic azides provided a mixture of regioisomers (Scheme 19).[22] Thus, regioselective synthesis of 1,4,5–trisubstituted 1,2,3–triazoles had to be investigated. The synthetic strategy of 1,4,5–trisubstituted 1,2,3–triazoles via direct arylation of easily available 1,4–disubstituted 1,2,3–triazoles seems to be ideal.

Scheme 19.

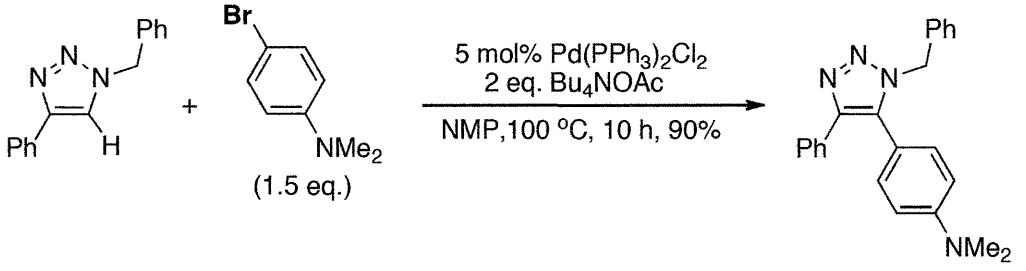


2–1. Palladium–Catalyzed Direct Arylation Reaction of 1,2,3–Triazole with Aryl Halides

In 2007, Gevorgyan and co–workers reported the first direct arylation reactions of 1,2,3–triazoles (Scheme 20).[23] They have shown that a variety of unsymmetrically substituted 1,2,3–triazoles can be easily synthesized via Pd–catalyzed direct arylation of 1,4–disubstituted triazoles, compounds that are readily accessible via "click" chemistry. Although arylation

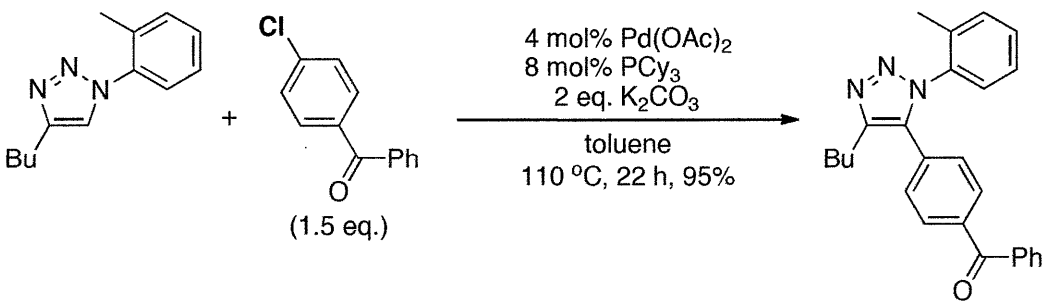
reactions proceeded with excellent efficiency, providing a variety of 1,4,5–trisubstituted 1,2,3–triazoles, each reaction required aryl bromides and a prolonged reaction time.

Scheme 20.



Among aryl halides, aryl chlorides are arguably the most useful class of electrophilic substrates due to their lower costs and a wide diversity of commercially available compounds. Generally, there are not so many examples of applicable methodologies for the use of aryl chlorides in catalytic direct arylations through C–H bond cleavages.[17] This is also the case for direct arylation of 1,2,3–triazoles, and only one example had been reported (Scheme 21).[24] This reaction also required a prolonged time to complete.

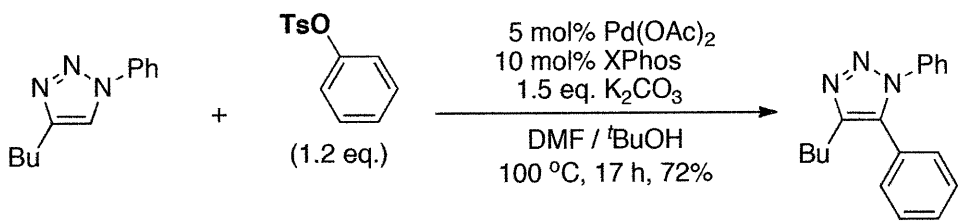
Scheme 21.



The use of aryl tosylates or mesylates as electrophilic arylating reagents in cross–coupling chemistry is highly desirable because they can be prepared from readily available phenols or ketones and inexpensive reagents and because of their moisture–stable and highly crystalline nature. Unfortunately, their improved stabilities translate into significantly reduced reactivities

in catalytic coupling chemistry. As a result, methodologies for catalyzed direct arylations through C–H bond cleavages with these convenient sulfonates had not previously been reported.[25] Recently, Ackermann and co–workers disclosed that aryl tosylates were amenable to palladium–catalyzed direct arylation of 1,4–disubstituted 1,2,3–triazoles (Scheme 22).[26]

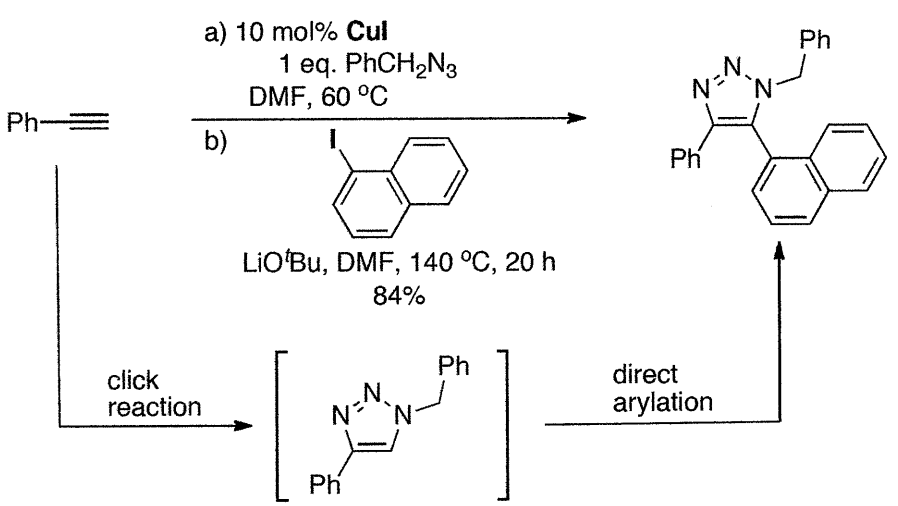
Scheme 22.



2–2. Copper–Catalyzed Direct Arylation Reaction of 1,2,3–Triazole with Aryl Iodides

Inexpensive copper catalysts can also realize direct arylation of 1,4–disubstituted 1,2,3–triazoles with aryl iodides (Scheme 23).[27] Advantageously, copper–catalyzed reactions allowed modular one–pot multicomponent syntheses of fully decorated triazoles through a sustainable "click" reaction/direct arylation sequence, starting from aryl iodides, alkynes and organic azides.[27a]

Scheme 23.



3. Overview of This Thesis

As described above, the palladium–catalyzed transformation reactions of commercially available aryl halides are attractive. The author focused on new synthetic reactions of aryl halides with homoallyl alcohols or triazoles under palladium catalysis. In Chapters 1–4, the syntheses of various compounds via retro–allylation strategy are described. In Chapter 5, the highly efficient syntheses of 1,4,5–trisubstituted 1,2,3–triazoles are presented. Both are important transformation reactions of aryl halides.

3–1. Palladium–Catalyzed Reactions of Aryl Halides with Homoallyl Alcohols (Chapters 1–4)

Allylation reaction with allylmetal reagents is one of the most powerful and useful methods in organic synthesis. However, most allylmetal reagents are air– and moisture–sensitive and thus are not so easy to handle. Homoallyl alcohols are emerging as allylmetal equivalents in palladium–catalyzed allylation via retro–allylation (Section 1–7). Taking advantage of the retro–allylation strategy, the author also discovered that the regio– and stereoselective synthesis of alkenes that are hard to prepare.

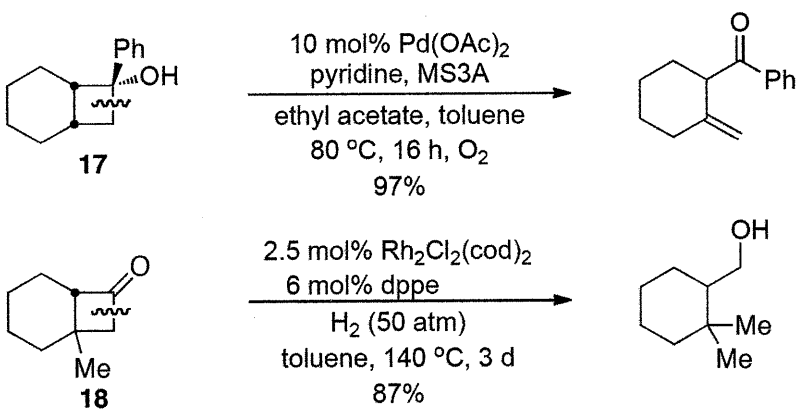
3–1–1. Palladium–Catalyzed Arylative Ring Opening Reaction of Cyclic Homoallyl Alcohols with Aryl Halides via Retro–Allylation (Chapter 1)

In Chapter 1, the author describes the palladium–catalyzed ring opening arylation reaction of cyclic homoallyl alcohols with aryl halides.

Recently, C–C bond cleavage reactions under transition metal catalysis have been developed. Especially, endocyclic C–C bond cleavage reactions of small rings have been well investigated (Scheme 24). For instance, Uemura reported that oxidative ring opening reaction of tertiary cyclobutanols such as **17** under palladium catalysis occurred, yielding the corresponding β,γ–unsaturated ketones.[16b,16c] Murakami also disclosed rhodium–catalyzed reductive ring opening reaction of cyclobutanones like **18**.[28] Cyclopropanes and cyclobutanes are highly

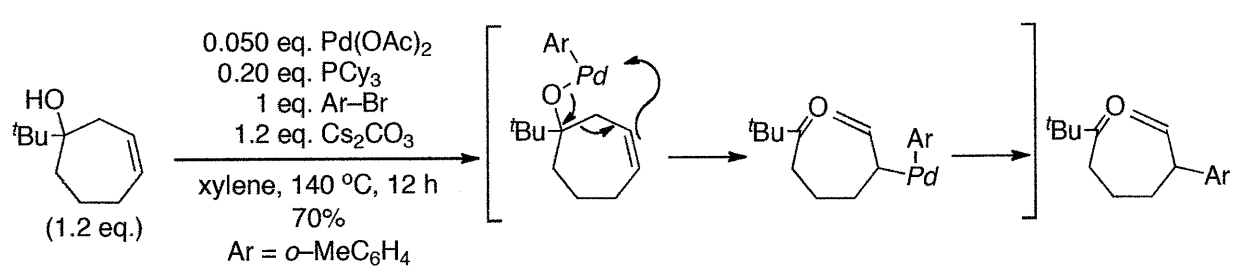
strained compounds. Therefore, ring opening reactions of such compounds easily occur. However, ring opening reactions of less strained compounds that have five–, six– and seven–membered ring skeleton were unknown.

Scheme 24.



In 2006, the palladium–catalyzed allylation reactions of aryl halides with homoallyl alcohols via palladium–catalyzed retro–allylation have been reported.[13] The author applied the retro–allylation reactions to the ring opening reactions of cyclic homoallyl alcohols. By starting from the homoallyl alcohols which have an endocyclic double bond, one can make the reactions proceed effectively to obtain the corresponding arylated unsaturated ketones (Scheme 25).

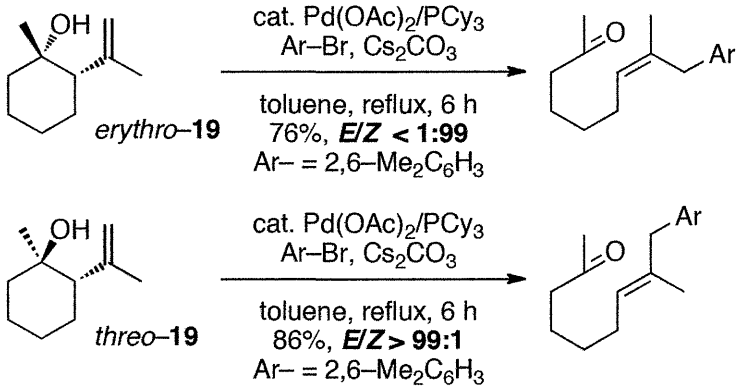
Scheme 25.



A different mode of ring opening reaction was investigated by using 2–alkenyl–substituted cyclohexanol derivatives. The reaction was found to proceed efficiently to yield the

corresponding arylated product. Interestingly, transformations of *erythro*– and *threo*–**19** provided the arylated unsaturated ketones stereospecifically with *Z* and *E* stereochemistry respectively (Scheme 26).

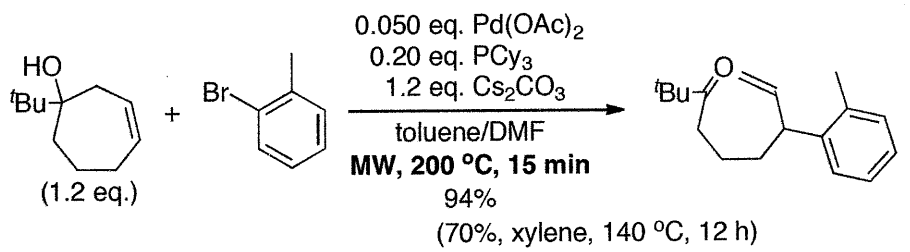
Scheme 26.



3–1–2. Microwave–Assisted Palladium–Catalyzed Allylation of Aryl Halides with Homoallyl Alcohols via Retro–Allylation (Chapter 2)

In Chapter 2, the author presents the palladium–catalyzed allylations of aryl halides with homoallyl alcohols via retro–allylation under microwave irradiation (Scheme 27). Although the palladium–catalyzed regio– and stereospecific allylation of aryl halides via retro–allylation of homoallyl alcohols is useful in organic synthesis, the reaction required a long time to complete, which represents a significant drawback. In order to shorten the reaction time, the same reactions were investigated at high temperatures such as 200 °C under microwave irradiation. As a result, the reactions were completed within 15 minutes, which is huge improvement from the overnight reflux conditions. This dramatic rate enhancement can be attributed to the acceleration of the rate–determing retro–allylation step at high temperatures. Interestingly, the reactions proceeded with high regio– and stereoselectivity even at high temperature.

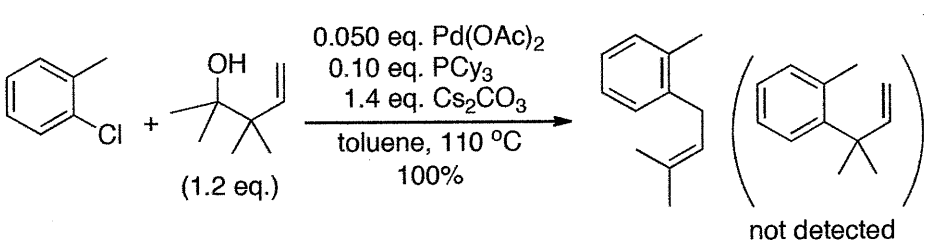
Scheme 27.



3–1–3. Synthesis of Prenylarenes and Related (Multisubstituted Allyl)arenes from Aryl Halides and Homoallyl Alcohols via Palladium–Catalyzed Retro–Allylation (Chapter 3)

In Chapter 3, the author describes the application of the allylation with homoallyl alcohols to the synthesis of (multisubstituted allyl)arenes (Scheme 28). Prenyl–substituted arenes are often found in natural products, most of which show significant biological activities. The synthesis of such biologically interesting compounds has hence been well investigated. However, the construction of prenylarene skeletons is usually diffcult. In most cases, the conventional cross–coupling reactions of aryl halides with prenylmetal reagents provide a mixture of regioisomers. Regioselective, convenient, and reliable prenylation reactions of aryl halides are unknown. The author studied prenylation reactions and related reactions that introduce multisubstituted allylic groups into aryl halides by making use of the retro–allylation strategy. The regioisomers were not detected in any cases.

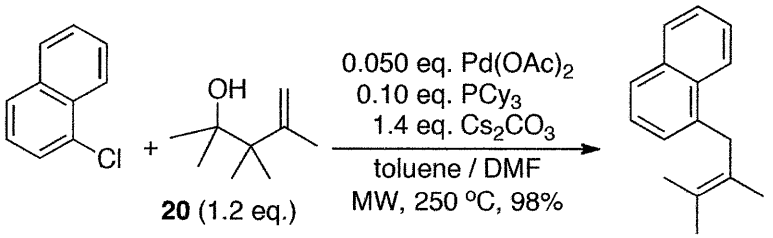
Scheme 28.



Reactions of aryl halides with alcohol **20** provided tetrasubstituted alkene through transposition of the double bond (Scheme 29). The reactions are high–yielding under

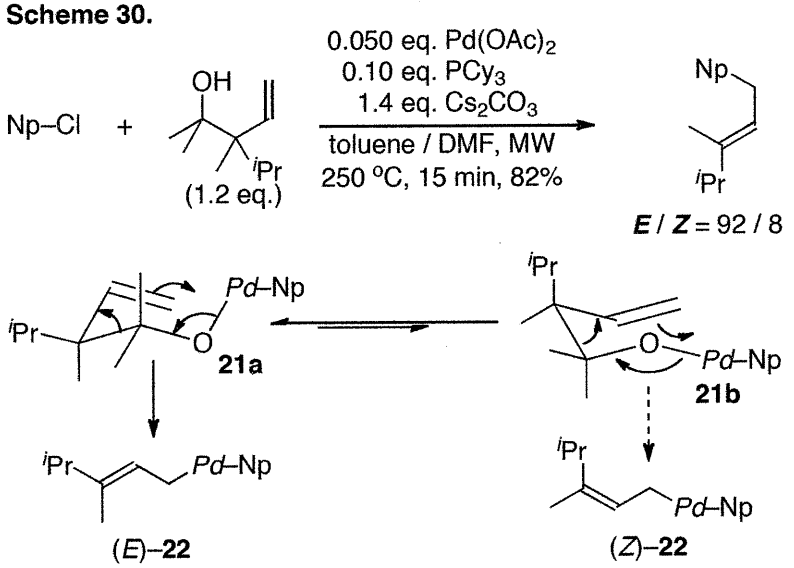
microwave irradiation at 250 °C. On the contrary, the preparation of such tetrasubstituted alkenes by conventional Wittig–type olefination often results in low yields.

Scheme 29.



Stereoselective synthesis of trisubstituted alkenes was performed by using the alcohol, which has two different substituents, methyl and isopropyl groups, at the allylic position. Formation of the E isomer predominated, and the stereoselectivity can be rationalized as shown in Scheme 30. During the retro–allylation step, a chairlike transition state **21a** would be most favorable because the isopropyl group would be located at the equatorial position. The other chairlike transition state **21b** has the isopropyl group at the axial position, which would render this transition state unfavorable. Formation of the transition state **21a** is thus preferred. The intermediate (*E*)–**22** finally undergoes smooth reductive elimination to yield the *E* isomer selectively.

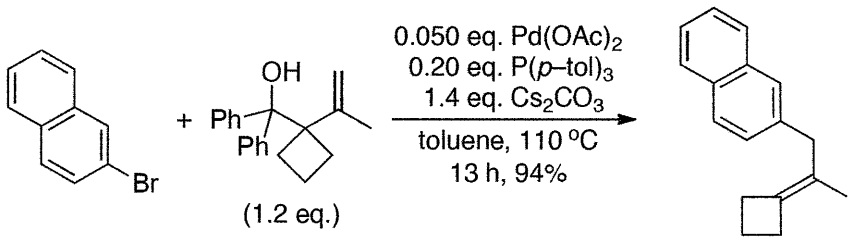
Scheme 30.



3–1–4. Synthesis of (2–Arylethylidene)cyclobutanes by Palladium–Catalyzed Reactions of Aryl Halides with Homoallyl Alcohols Bearing a Trimethylene Group at the Allylic Position (Chapter 4)

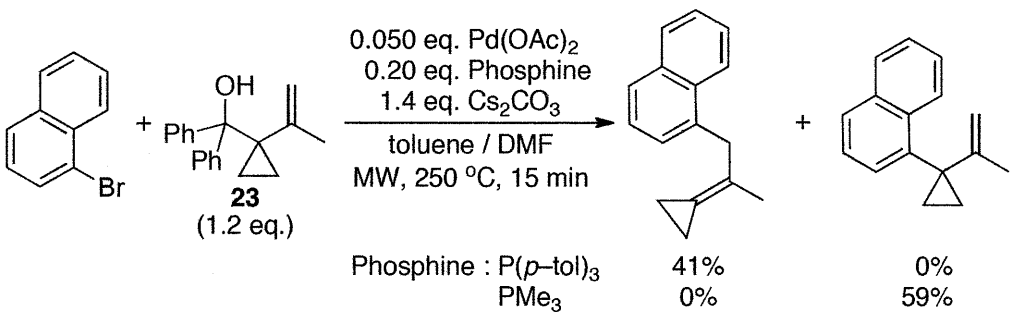
Alkylidenecyclobutanes are interesting compounds due to their strained skeleton and reactive double bonds and are hence useful in organic synthesis. Uncatalyzed and catalyzed cycloaddition reactions of allenes with activated alkenes represent conventionally the most useful method for the synthesis of alkylidenecyclobutanes. However, the requirement of activated alkenes limits the scope of the reactions. Thus, a new efficient method for constructing this intriguing strained skeleton has been required. In Chapter 4, the author reports the palladium–catalyzed allylation of aryl halides via retro–allylation of homoallyl alcohols bearing a trimethylene group at the allylic position, providing the corresponding alkylidenecyclobutanes (Scheme 31). The cyclobutane–containing homoallylic alcohol was easily synthesized from commercially available ethyl cyclobutanecarboxylate.

Scheme 31.



An extension of the cyclobutane synthesis led to the preparation of alkylidenecyclopropanes by using alcohol **23** (Scheme 32). The yields were moderate, even when the reaction was performed at 250 °C under microwave irradiation. Interestingly, the use of trimethylphosphine instead of tri–*p*–tolylphosphine reversed the regioselectivity, and vinylcyclopropane was obtained exclusively.

Scheme 32.



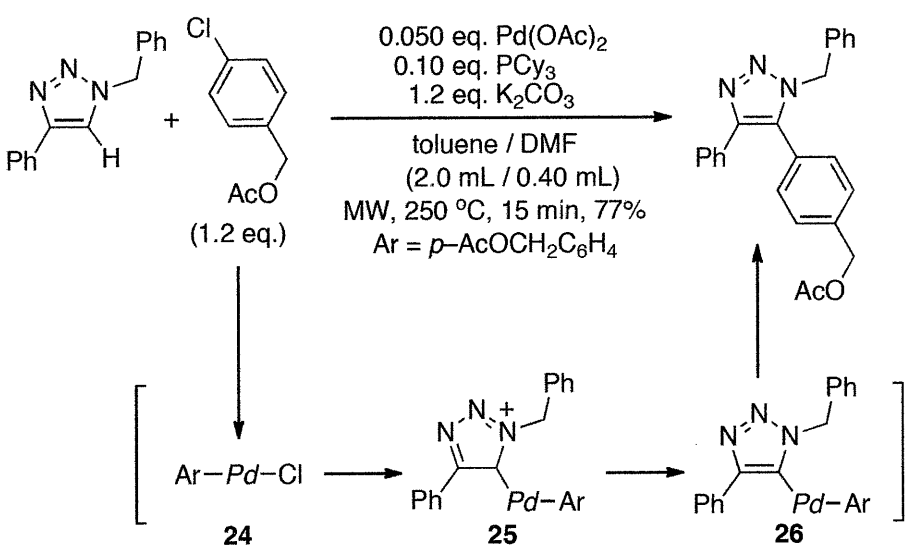
3–2. Microwave–Assisted Palladium–Catalyzed Direct Arylation of 1,4–Disubstituted 1,2,3–Triazoles with Aryl Chlorides (Chapter 5)

Transition–metal–catalyzed direct arylation reactions of aromatic compounds with aryl halides have attracted increasing attention. Unlike cross–coupling reactions, direct arylation reactions avoid the need for stoichiometric amounts of organometallic reagents, resulting in fewer reaction steps and reduced waste.

In Chapter 5, taking advantage of ready availability of 1,4–disubstituted triazoles by the copper–catalyzed reaction,[21a] the author reports palladium–catalyzed direct arylation of

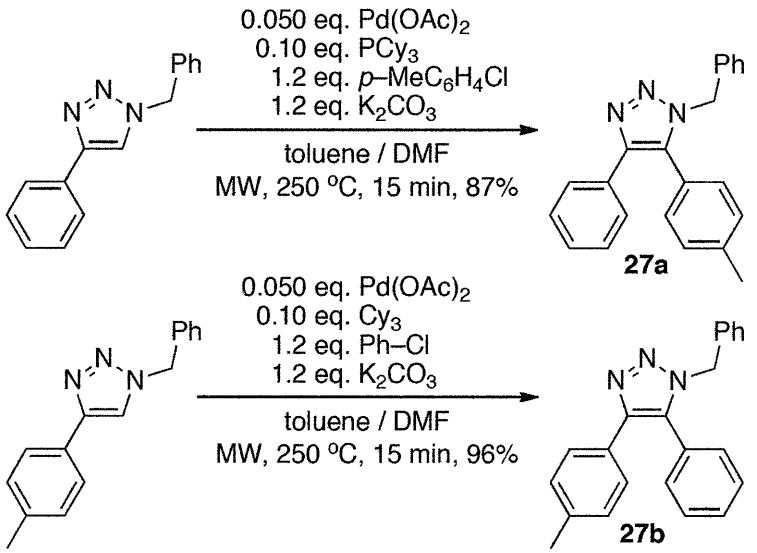
1,4–disubstituted triazoles with aryl chlorides. The arylation took place at the 5 position, representing a regioselective access to 1,4,5–trisubstituted triazoles. A combined use of tricyclohexylphosphine as the ligand and microwave heating at 250 °C allowed the author to employ aryl chlorides as arylating agents and to complete the reaction within only 15 min (Scheme 33). The reaction proceeds as follows: (1) oxidative addition of aryl chloride to zerovalent palladium; (2) nucleophilic substitution of 1,2,3–triazole with chloro(aryl)palladium complex **24** yielding aryl(triazolyl)palladium **26** via **25**; and (3) reductive elimination to yield the product.

Scheme 33.



The conventional method to prepare 1,4,5–trisubstituted 1,2,3–triazole from organic azide and internal alkyne provided a mixture of regioisomers.[22] However, by applying direct arylation reaction of 1,4–disubstituted 1,2,3–triazole, one can introduce structually and electronically analogous substituents regioselectively. For instance, the present approach to trisubstituted triazoles allowed for selective preparation of two regioisomers **27a** and **27b** (Scheme 34).

Scheme 34.



In summary, the author has developed new synthetic methods by using palladium–catalyzed reactions of aryl halides with tertiary homoallyl alcohols and with 1,4–disubstituted 1,2,3–triazoles. These works will lead to further progress of the chemistry of regio– and stereoselective synthesis and thus will be of use in the fields of material chemistry and medicinal chemistry as well as synthetic organic chemistry and organometallic chemistry.

References and Notes

1. (a) *Metal–Catalyzed Cross–Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley–VCH: Weinheim, 1998. (b) *Metal–Catalyzed Cross–Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley–VCH: Weinheim, 2004. (c) *Cross–Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.: Springer: Berlin, 2002. (d) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.
2. (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793.
3. Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958–1969.
4. (a) Obora, Y.; Tsuji, Y.; Kobayashi, M.; Kawamura, T. *J. Org. Chem.* **1995**, *60*, 4647–4649. (b) Takemura, Y.; Hirayama, A.; Tokunaga, J.; Kawamura, F.; Inagaki, K.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **1999**, *40*, 7501–7505.
5. Ligand effect on the regiochemistry of such couplings is discussed in detail: (a) Kurosawa, H.; Shiba, K.; Hirako, K.; Kakiuchi, K.; Ikeda, I. *J. Chem. Soc., Chem. Commun.* **1994**, 1099–1100. (b) Kurosawa, H.; Shiba, K.; Hirako, K.; Ikeda, I. *Inorg. Chim. Acta* **1996**, *250*, 149–154. (c) Kurosawa, H.; Ogoshi, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 973–984.
6. (a) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075–7076. (b) Hatanaka, K.; Goda, T.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6511–6514.
7. (a) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 16382–16393. (b) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2010**, *132*, 3612–3620.
8. (a) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 704–705. (b) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 1368–1369. (c) Yamamoto, Y.; Takada, S.; Miyaura, N.; Iyama, T.; Tachikawa, H. *Organometallics* **2009**, *28*, 152–160.
9. (a) Lee, P. H.; Sung, S.; Lee, K. *Org. Lett.* **2001**, *3*, 3201–3204. (b) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265–8268.

10. (a) Knölker, H.–J.; Fröhner, W. *Synlett* **1997**, 1108–1110. (b) Fröhner, W.; Reddy, K. R.; Knölker, H. –J. *Heterocycles* **2007**, *74*, 895–912. (c) Knölker, H. –J. *Chem. Lett.* **2009**, *38*, 8–13.

11. (a) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Tetrahedron* **1989**, *45*, 1067–1078. (b) Roberts, R. M. G. *J. Organomet. Chem.* **1969**, *18*, 307–319.

12. (a) Numata, S.; Okawara, R.; Kurosawa, H. *Inorg. Chem.* **1977**, *16*, 1737–1741. (b) Solin, N.; Kjellgren, J.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026–7033. (c) García–Iglesias, M.; Buñuel, E.; Cárdenas, D. J. *Organometallics* **2006**, *25*, 3611–3618.

13. Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, *K. J. Am. Chem. Soc.* **2006**, *128*, 2210–2211.

14. Zirconium–mediated reactions: (a) Fujita, K.; Yorimitsu, H.; Oshima, K. *Chem. Rec.* **2004**, *4*, 110–119. (b) Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2004**, *69*, 3302–3307. Gallium–mediated reactions: (c) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2005**, *7*, 3577–3579. (d) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Organomet. Chem.* **2007**, *692*, 505–513. Rhodium–catalyzed reactions: (e) Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 2515–2517. (f) Jang, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* **2007**, *48*, 4003–4005. (g) Sumida, Y.; Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2008**, *3*, 119–125. (h) Zhao, P.; Incarvito, C. D.; Hartwig, J. F.; *J. Am. Chem. Soc.* **2006**, *128*, 9642–9643. (i) Shintani, R.; Takatsu, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 1191–1193. Nickel–catalyzed reaction: (j) Sumida, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 1629–1632.

15. Retro–allylations from lithium, magnesium, tin, and zinc alkoxides were observed: (a) Benkeser, R. A.; Broxterman, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 5162–5163. (b) Benkeser, R. A.; Siklosi, M. P. *J. Org. Chem.* **1976**, *41*, 3212–3213. (c) Benkeser, R. A.; Siklosi, M. P.; Mozdzen, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134–2139. (d) Miginiac, P. *Bull. Chim. Soc. Fr.* **1970**, 1077–1083. (e) Gerard, F.; Miginiac, P. *Bull. Chim. Soc. Fr.* **1974**, 1924–1930. (f) Gerard, F.; Miginiac, P. *Bull. Chim. Soc. Fr.* **1974**, 2527–2533. (g) Barbot,

F.; Miginiac, P. *Bull. Chim. Soc. Fr.* **1977**, 113–116. (h) Barbot, F.; Miginiac, P. *J. Organomet. Chem.* **1977**, *132*, 445–454. (i) Holm, T. *Acta Chem. Scand. B* **1976**, *30*, 985–990. (j) Snowden, R. L.; Schulte–Elte, K. H. *Helv. Chim. Acta* **1981**, *64*, 2193–2202. (k) Jones, P.; Millot, N.; Knochel, P. *Chem. Commun.* **1998**, 2405–2406. (l) Jones, P.; Knochel, P. *Chem. Commun.* **1998**, 2407. (m) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186–195. (n) Millot, N.; Knochel, P. *Tetrahedron Lett.* **1998**, *40*, 7779–7782. (o) Peruzzo, V.; Tagliavini, G. *J. Organomet. Chem.* **1978**, *162*, 37–44. (p) Gambaro, A.; Marton, D.; Peruzzo, V.; Tagliavini, G. *J. Organomet. Chem.* **1981**, *204*, 191–196. (q) Yanagisawa, A.; Aoki, T.; Arai, T. *Synlett* **2006**, 2071–2074. Ruthenium–catalyzed deallylation was reported: (r) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587–5588. (s) Kondo, T.; Mitsudo, T. *Chem. Lett.* **2005**, *34*, 1462–1467.

16. Palladium–catalyzed reactions of organic halides with tertiary alcohols via β–carbon elimination were reported. Arylation with arylmethanols: (a) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407–10408. Via ring opening of cyclobutanols: (b) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010–11011. (c) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (d) Larock, R. C.; Reddy, C. K. *Org. Lett.* **2000**, *2*, 3325–3327. Alkynylation with propargylic alcohols: (e) Chow, H.–F.; Wan, C.–W.; Low, K.–H.; Yeung, Y.–Y. *J. Org. Chem.* **2001**, *66*, 1910–1913.
17. *Modern Arylation Methods*, Ackermann, L., Ed.; Wiley–VCH, Weinheim, 2009.
18. (a) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413. (b) Chen, X. Engle, K. M.; Wang, D.–H.; Yu, J.–Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (c) Thansamdote, P.; Lautens, M. *Chem. Eur. J.* **2009**, *15*, 5874–5883. (d) Daugulis, O.; Do, H.–Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (e) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (f) Li, B.–J.; Yang, S.–D.; Shi, Z.–J. *Synlett* **2008**, 949–957. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (h) Satoh, T.; Miura,

M. *Chem. Lett.* **2007**, *36*, 200–205. (i) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (j) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (k) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727–2734. (l) Campeau, L.–C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41. (m) Ackermann, L. *Synlett* **2007**, 507–526.

19. (a) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (b) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55–83. (c) *Handbook of C–H Transformations*; Dyker, G., Ed.; Wiley–VCH: Weinheim, 2005. (d) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470. (e) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283–3307.
20. Nakamura, N.; Tajima, Y.; Sakai, K. *Heterocycles* **1982**, *17*, 235–245.
21. (a) Rostotsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.
22. Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680–8683.
23. Chuprakov, S.; Chernyak, N.; Dudnik A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *12*, 2333–2336.
24. Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741–748.
25. For selected examples of palladium–catalyzed traditional coupling reactions of aryl tosylates with organometallic reagents, see: (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819. (b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. (c) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704–8705. (d) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250–12251. (e) Ebran, J.–P.; Hansen, A. L.; Gogsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931–6942. (f) Hansen, A. L.; Ebran, J.–P.; Ahlquist, M.; Norrby, P.–O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349–3353. (g) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993–5996. (h) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754–2755 and refs. cited therein.

26. Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201–204.

27. (a) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084. (b) Fukuzawa, S.; Shimizu, E.; Ogata, K. *Heterocycles* **2009**, *78*, 645–655.

28. Murakami, M.; Amii, H.; Shigeto, K.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8285–8290.

Chapter 1

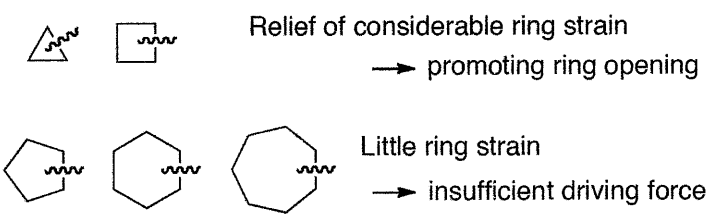
Palladium–Catalyzed Arylative Ring Opening Reaction of Cyclic Homoallyl Alcohols with Aryl Halides via Retro–Allylation

Arylative ring opening reactions of less strained cyclic homoallyl alcohols take place upon treatment with aryl bromides in the presence of cesium carbonate and a palladium catalyst. The ring opening process includes retro–allylation, which proceeds via a conformationally regulated six–membered transition state. The reaction hence proceeds with excellent regio– and stereospecificity, yielding ketones having an allylarene moiety.

Introduction

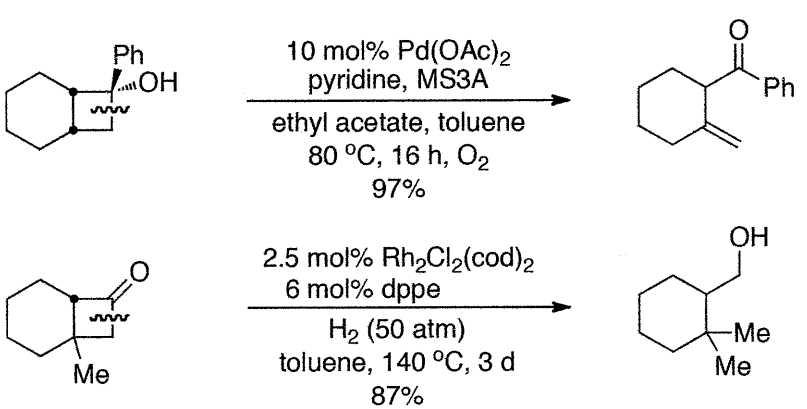
Recently, C–C bond cleavage reactions under transition metal catalysis have been attracting increasing attention. Especially, endocyclic C–C bond cleavage reactions of small rings have been well investigated (Scheme 1).[1] Whereas highly strained small rings as cyclopropanes and cyclobutanes easily underwent the ring opening reaction, ring opening reactions of less strained compounds which have five–, six– and seven–membered ring skeleton are rare.

Scheme 1.



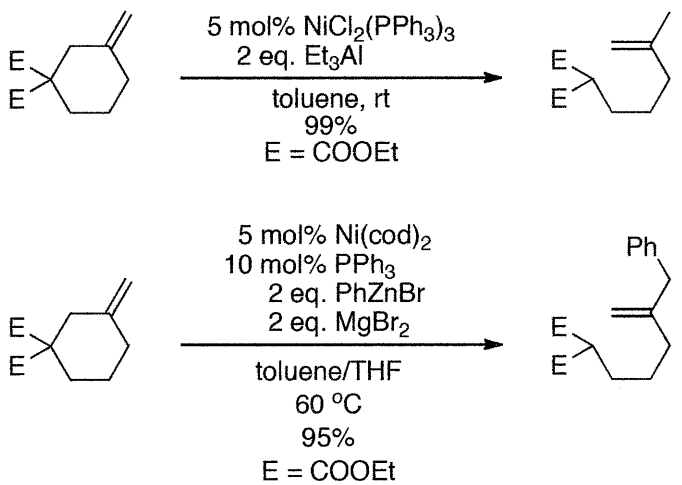
For instance, Uemura[2] and Murakami[3] reported ring opening of cyclobutanes framework under palladium and rhodium catalysis, respectively (Scheme 2). In addition to these reactions, a large number of noteworthy examples of cleavages of strained rings under transition–metal catalysis have been reported.[1]

Scheme 2.



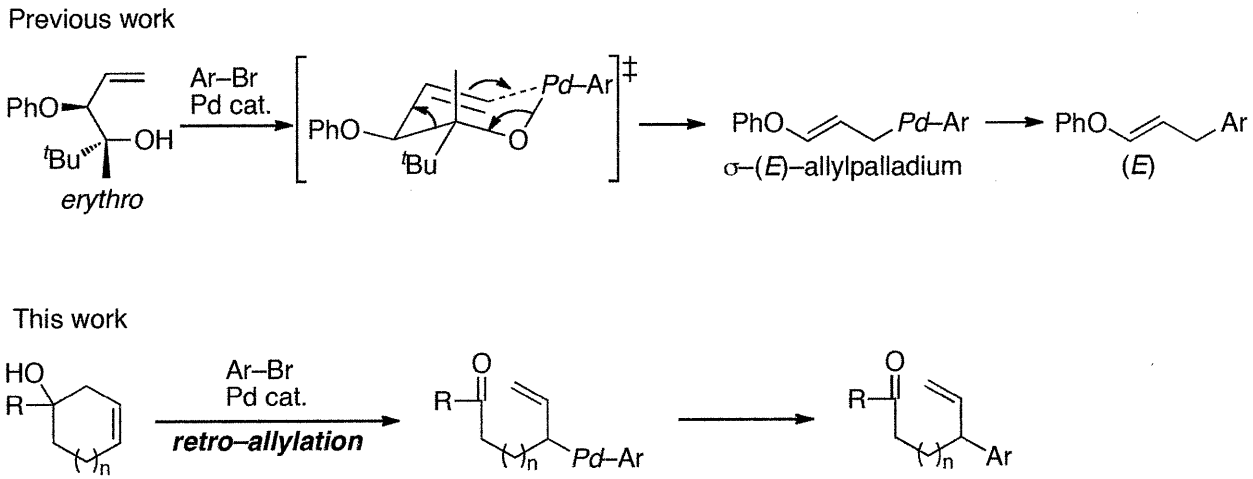
In contrast, ring opening reactions of unstrained compounds are still difficult due to their stability. Kotora showed ring opening of unstrained methylenecycloalkanes via deallylation of allylmalonate under nickel catalysis.[4] Nickel–catalyzed arylative ring opening reactions of methylenecycloalkanes with arylzinc reagents have been also reported by Oshima (Scheme 3).[5] Other than these reactions, cleavages of such unstrained rings are rarely known.

Scheme 3.



Very recently, regio– and stereospecific allylation reactions of aryl halides via palladium–catalyzed retro–allylation of homoallyl alcohols have been reported.[6] In Chapter 1, the author reports arylative ring opening reactions by making use of retro–allylation strategy (Scheme 4). The palladium–catalyzed retro–allylation reactions reported so far are allyl transfer reactions from acyclic homoallyl alcohols, which inherently accompany the loss of the corresponding ketone. The author chose cyclic homoallyl alcohols as substrates. Properly designed homoallyl alcohols can be transformed into σ–allyl(aryl)palladium intermediates that have an intramolecular keto group. The reactions of such homoallyl alcohols proceed without loss of any carbon units.

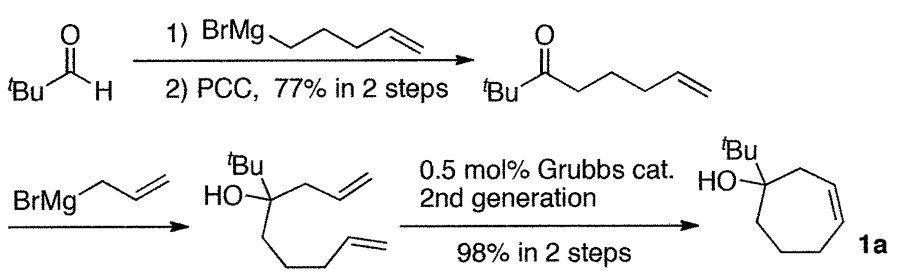
Scheme 4.



Results and Discussion

To begin with, cycloheptenol **1a** was prepared in four steps. The synthesis consists of (1) nucleophilic addition of 4–pentenylmagnesium bromide to pivalaldehyde, (2) oxidation with pyridinium chlorochromate, (3) nucleophilic allylation of the resulting ketone, and (4) ruthenium–catalyzed ring closing metathesis (Scheme 5). Each step was facile and robust, and thus endocyclic homoallyl alcohol **1a** was readily accessible.

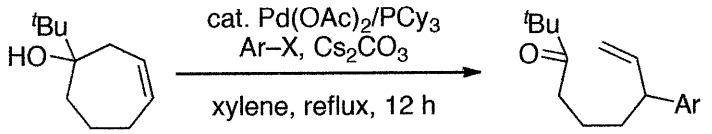
Scheme 5.



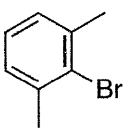
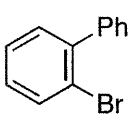
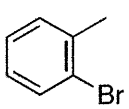
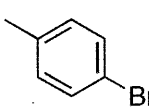
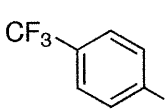
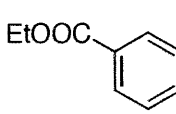
Cycloheptenol **1a** was subjected to the palladium–catalyzed reactions with various aryl bromides (Table 1). The arylative ring–opening reactions were regiospecific, providing terminal unsaturation. The reactions required a higher temperature in refluxing xylene,

compared to allyl transfer reaction.[6] The more restricted conformation of **1a**, compared to that of acyclic homoallyl alcohols, would cause weaker interaction between the palladium and the double bond in the corresponding palladium alkoxide (Figure 1). Tricyclohexylphosphine, three equimolar amounts to palladium, was the best ligand, and triphenylphosphine was not so effective (entry 5). The *tert*–butyl group of **1a** was essential to attain satisfactory yields. The reaction of the isopropyl analogue **1b** furnished the corresponding product **3g** in only 20% yield (eq 1). Cyclohexenol **1c** underwent similar ring–opening reaction efficiently, wherein PPh_3 was exceptionally the better ligand (eq 2).

Table 1. Arylative Ring–Opening Reactions of 1–*tert*–Butyl–3–cyclohepten–1–ol (**1a**)[a]

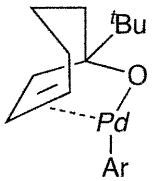


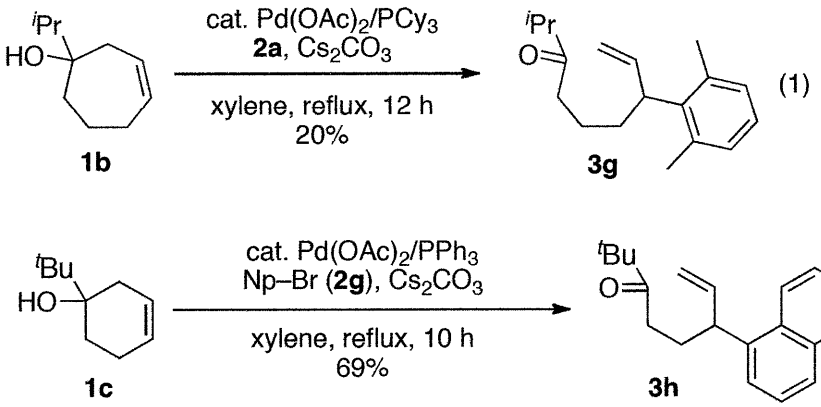
1a **3**

entry	Ar–Br **2**	yield (%)
1	 **2a**	**3a**, 80
2	 **2b**	**3b**, 68
3	 **2c**	**3c**, 70
4	 **2d**	**3d**, 65
5	**2d**	**3d**, <10[b]
6	 **2e**	**3e**, 64
7	 **2f**	**3f**, 46

[a] $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.075 mmol), Cs_2CO_3 (0.72 mmol), **1a** (0.60 mmol), and **2** (0.50 mmol) were used. [b] PPh_3 (0.10 mmol) was used instead of PCy_3 (0.075 mmol).

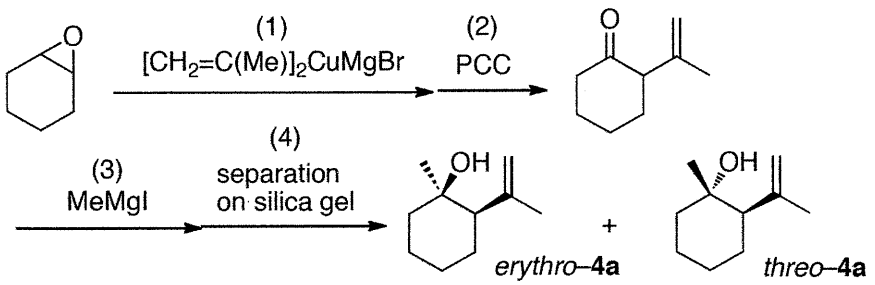
Figure 1. One of the possible modes of interaction between the palladium and the double bond of **1a**





The author next prepared *erythro*– and *threo*–2–isopropenyl–1–methylcyclohexanol (**4a**).[7] Homoallyl alcohol **4a** was synthesized in four steps: (1) the reaction of cyclohexene oxide with di(isopropenyl)cuprate, (2) oxidation by PCC, and (3) methylation of the resulting carbonyl group (Scheme 6). The methylation provided a mixture of *erythro*–**4a** and *threo*–**4a** in a ratio of 10:1, which was (4) chromatographed on silica gel to isolate each isomer.

Scheme 6.



Both isomers *erythro*–**4a** and *threo*–**4a** underwent smooth ring–opening with excellent regio– and stereospecificity (Table 2). The reactions represent novel synthesis of ketones involving extremely remote arylation. The high stereoselectivity would stem from bicyclic, decalin–like transition states **6** (Scheme 7).

Scheme 7.

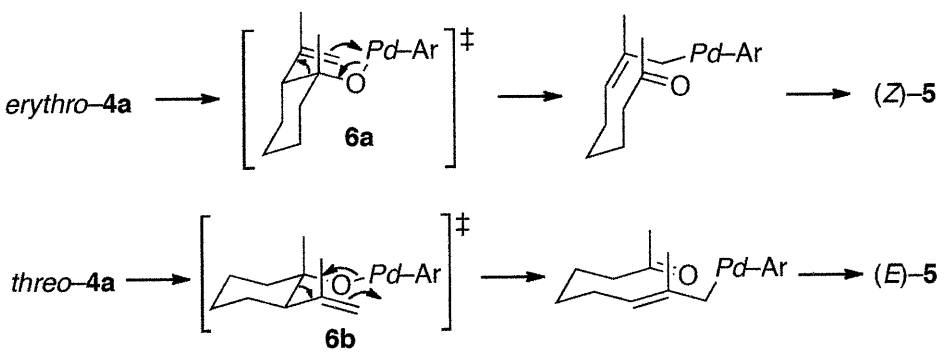
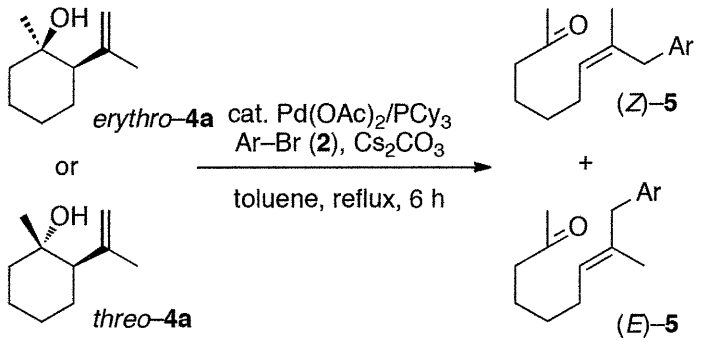
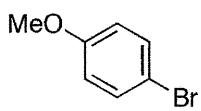


Table 2. Arylative Ring–Opening Reactions of *erythro*– and *threo*–2–Isopropenyl–1–methylcyclohexanol (**4a**)[a]

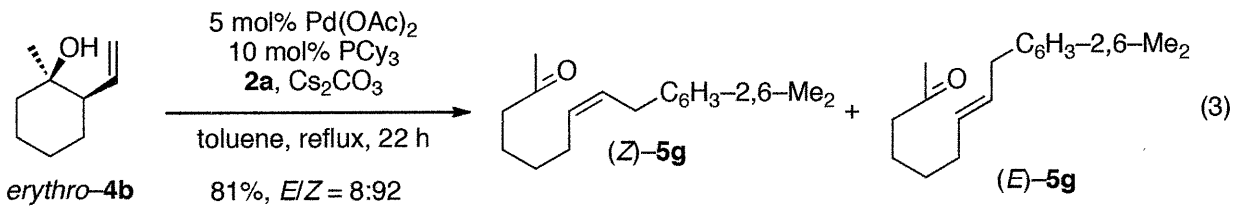


entry	*erythro*/*threo*–**4a**	**2**	**5**	yield (%) (*E*/*Z*)
1	*erythro*	**2a**	**5a**	76 (<1:99)
2	*erythro*	**2e**	**5b**	54 (<1:99)
3	*erythro*	**2f**	**5c**	81 (<1:99)
4	*erythro*	 **2h**	**5d**	61[b] (<1:99)
5	*erythro*	**2c**	**5e**	64 (<5:95)
6	*erythro*	**2d**	**5f**	84 (<5:95)
7	*threo*	**2a**	**5a**	86 (>99:1)
8	*threo*	**2d**	**5f**	71 (>95:5)

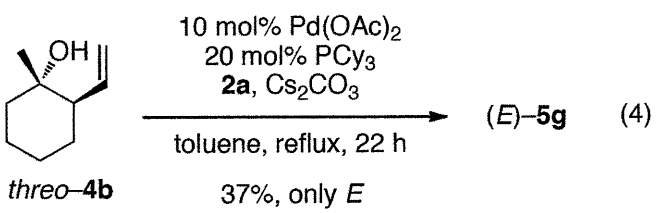
[a] $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.075 mmol), Cs_2CO_3 (0.60 mmol), **4a** (0.50 mmol), and **2** (0.60 mmol) were used. [b] Performed for 22 h.

Alcohol **4b** having a vinyl group also underwent stereospecific ring–opening. In the reaction of *erythro*–**4b** (eq 3), slightly lower yet still satisfactory stereoselectivity was observed, compared to the reaction of *erythro*–**4a** (Table 2, entry 1). The stereoselectivity was perfect in

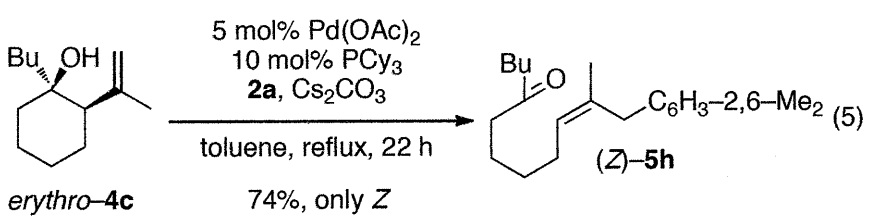
the reaction of *threo*–**4b** albeit the conversion of *threo*–**4b** was low even with an increasing amount of the catalyst (eq 4). Synthesis of butyl ketone (*Z*)–**5h** was also successful starting from *erythro*–**4c** (eq 5).



erythro–**4b**



threo–**4b**



erythro–**4c**

Conclusion

The author has applied the palladium–catalyzed ally transfer reaction to ring opening of less strained cyclic compound. The ring opening reaction leads to the regio– and stereospecific synthesis of ketones having a branched or linear allylarene unit at the remote terminus, starting from cyclic homoallylic alcohols.

Experimental Section

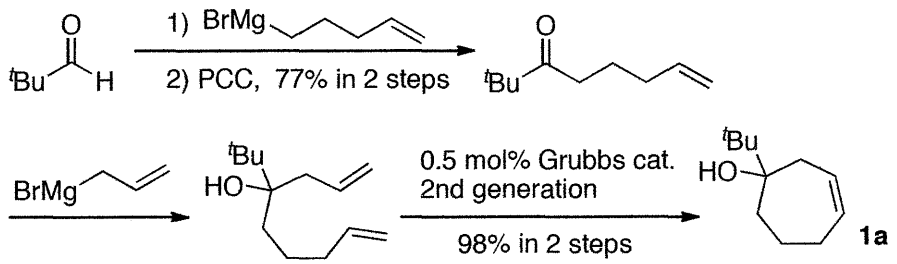
Instrumentation

^{1}H NMR (300 MHz and 500 MHz) and ^{13}C NMR (75.3 MHz and 125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.0 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR–8200PC spectrometer. Mass spectra (EI unless otherwise noted) were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25–mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Chemicals

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene and xylene were purchased from Wako Pure Chemical Co. and stored over slices of sodium. Tri(*p*–tolyl)phosphine, triphenylphosphine, and cesium carbonate were purchased from Wako Pure Chemical Co. Palladium acetate and tricyclohexylphosphine were from TCI. Grubbs catalyst, 2nd generation (benzylidene[1,3–bis(2,4,6–trimethylphenyl)–2–imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium) was purchased from Aldrich. The preparations of the homoallyl alcohols **1** are described in the following section. All reactions were carried out under argon atmosphere.

Preparation of endocyclic homoallyl alcohol 1a



Under an atmosphere of argon, 4–pentenylmagnesium bromide (1.0 M THF solution, 25 mL, 25 mmol) was placed in a 100–mL reaction flask. Pivalaldehyde (2.17 mL, 20 mmol) was added to the Grignard reagent dropwise at 0 °C. The mixture was warmed to room temperature and was stirred for 1.5 h. The reaction mixture was poured into saturated ammonium chloride solution (30 mL). The product was extracted with hexane (30 mL × 3), and organic layers were washed with brine. The combined organic layer was dried over sodium sulfate, and concentrated in vacuo to afford 2,2–dimethyl–7–octen–3–ol as a crude oil.

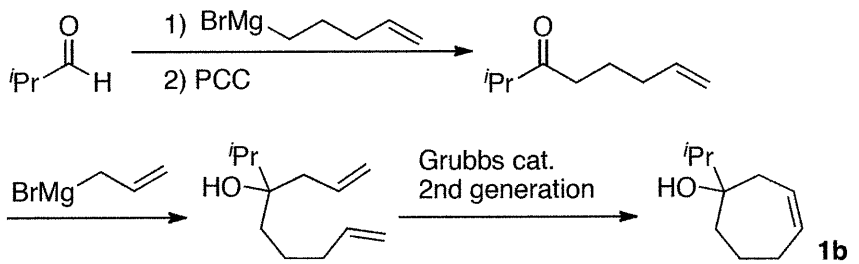
PCC (4.89 g, 22.6 mmol) and silica gel (4.9 g, Wakogel 200 mesh) were mixed in a mortar. The mixture was transferred to a 100–mL reaction flask. A solution of the crude alcohol in dichloromethane (57 mL) was then charged. The mixture was stirred for 6 h at ambient temperature. The mixture was filtered through a pad of Celite. The pad was washed with hexane and ether. After evaporation, the residue was passed through a pad of silica gel with ether as an eluent to remove chromium compounds. The corresponding ketone was obtained in 77% yield (2.36 g, 15.3 mmol).

Allylmagnesium bromide (0.77 M ethereal solution, 12.9 mL, 9.9 mmol) was placed in a 100–mL reaction flask under argon. The ketone (1.3 g, 8.2 mmol) in THF (8.2 mL) was added dropwise at 0 °C. After being stirred for 1.5 h at ambient temperature, the mixture was poured into saturated ammonium chloride solution (30 mL). The product was extracted with ethyl acetate (20 mL × 3), and organic layers were washed with brine. The combined organic layer was dried over sodium sulfate, and evaporated in vacuo to yield 4–*tert*–butyl–1,8–nonadien–4–ol.

The crude tertiary alcohol was dissolved in dichloromethane (30 mL) under argon.

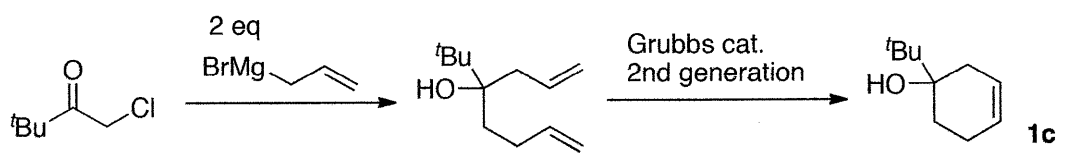
Grubbs catalyst, 2nd generation (34 mg, 0.038 mmol) was added to the solution. After being stirred for 20 h at room temperature, the mixture was filtered through a pad of Florisil. Evaporation followed by silica gel column purification (hexane/ether = 10:1) afforded **1a** (1.35 g, 8.05 mmol, 98%).

Preparation of 1b



Isopropyl–substituted alcohol **1b** was prepared in a fashion similar to the preparation of **1a**. The Grignard addition followed by the oxidation provided 2.42 g of 2–methyl–7–octen–3–one (17.3 mmol, 87% yield). The allylation of the ketone proceeded quantitatively. The final ring–closing metathesis provided 401 mg of **1b** (2.60 mmol, 77%) starting from 612 mg (3.36 mmol) of the dienol.

Preparation of 1c

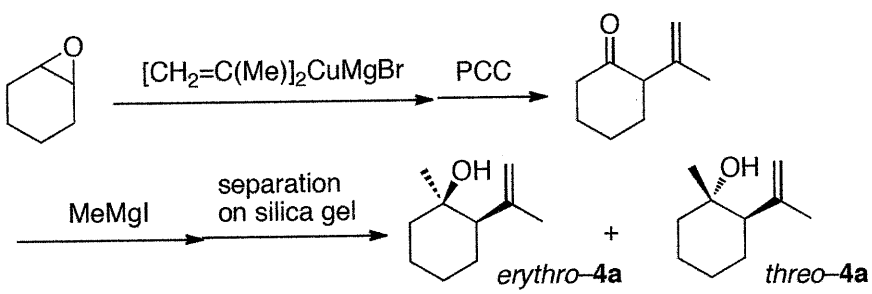


Under an atmosphere of argon, allylmagnesium bromide (0.85 M THF solution, 26 mL, 22 mmol) was placed in a 100–mL reaction flask. 1–Chloro–3,3–dimethyl–2–butanone (1.31 mL, 10 mmol) was added to the solution dropwise at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 4.5 h. The reaction mixture was poured into saturated ammonium chloride solution (30 mL), and the product was extracted with ethyl acetate (30 mL × 3). The combined organic layer was dried and concentrated. Alcohol,

4–*tert*–butyl–1,7–octadien–4–ol, was obtained as a crude oil.

The crude tertiary alcohol was treated with Grubbs catalyst, 2nd generation (45 mg, 0.050 mmol) in dichloromethane (40 mL) for 20 h at room temperature under argon. The mixture was filtered through a pad of Florisil, and the filtrate was evaporated. The product was chromatographed on silica gel (hexane/ether = 5:1) to afford **1c** (1.53 g, 9.90 mmol, 99%).

Preparation of *erythro*– and *threo*–4a



Copper(I) iodide (1.07 g, 5.63 mmol) was placed in a 300–mL reaction flask. THF (100 mL) and 1,2–epoxycyclohexane (5.64 mL, 56.3 mmol) were added. After the mixture was cooled to –40 °C, isopropenylmagnesium bromide (1.0 M THF solution, 113 mL, 113 mmol) was added through a dropping funnel. The mixture was allowed to warm to –20 °C, and stirred for 20 h. The reaction mixture was poured into saturated ammonium chloride solution (200 mL). The product was extracted with hexane (200 mL × 3), and each organic layer was washed with brine. The combined organic layer was dried over sodium sulfate, and concentrated in vacuo to afford 2–isopropenylcyclohexanol as a crude oil.

PCC (14.0 g, 64.7 mmol) and silica gel (14 g, Wakogel 200 mesh) were mixed in a mortar. The mixture was placed in a 300–mL reaction flask. A solution of the crude alcohol in dichloromethane (162 mL) was then charged under argon. The mixture was stirred for 12 h at room temperature. The mixture was filtered through a pad of Celite. The filtrate was evaporated in vacuo. Silica gel column chromatography (hexane/ether = 5:1) yielded 6.60 g of 2–isopropenylcyclohexanone (47.8 mmol, 85% yield).

Methylmagnesium iodide (1.0 M ethereal solution, 57.4 mL, 57.4 mmol) was placed in a

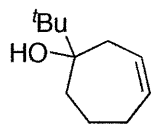
200–mL reaction flask under argon. The ketone (6.60 g, 47.8 mmol) in THF (50 mL) was added dropwise at 0 °C. After being stirred for 1.5 h at 0 °C, the mixture was poured into saturated ammonium chloride solution (100 mL). Extraction with hexane (100 mL × 3), concentration, and silica gel column purification (hexane/ethyl acetate = 20:1) provided *erythro*–**4a** (5.62 g, 36.4 mmol, 76%) and *threo*–**4a** (0.54 g, 3.5 mmol, 7.4%). The relative stereochemistry was determined by comparing ^{1}H and ^{13}C NMR data of closely related cyclic alcohols in the literature.[1]

Alcohols **4b** and **4c** were prepared in similar fashions.

Characterization Data

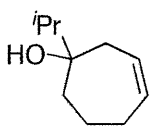
Compounds *erythro*–**4b** and *threo*–**4b** were known compounds.[8]

1–(*tert*–Butyl)–3–cyclohepten–1–ol (1a)



IR (neat) 3581, 2958, 1654, 1480, 1367, 1205, 1071, 980, 923, 854, 820, 761, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 9H), 1.52–1.60 (m, 1H), 1.63–1.70 (m, 1H), 1.71–1.76 (m, 1H), 1.80 (bs, 1H), 1.88–1.93 (m, 1H), 2.07–2.14 (m, 1H), 2.19–2.26 (m, 1H), 2.28–2.33 (m, 1H), 2.43 (ddd, *J* = 15.0, 8.5, 2.0 Hz, 1H), 5.51–5.56 (m, 1H), 5.95–6.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.29, 25.44, 29.21, 33.73, 37.22, 38.53, 75.45, 126.52, 135.31. Found: C, 78.55; H, 12.19%. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98%.

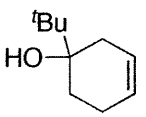
1–Isopropyl–3–cyclohepten–1–ol (1b)



IR (neat) 3420, 2840, 1456, 989 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, *J* = 5.0 Hz, 3H), 0.90 (d, *J* = 5.0 Hz, 3H), 1.50–1.54 (m, 2H), 1.66–1.72 (m, 2H), 1.81–1.86 (m, 2H), 2.05–2.12 (m, 1H),

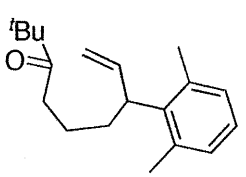
2.14–2.25 (m, 2H), 2.31–2.35 (m, 1H), 5.57–5.62 (m, 1H), 5.94–5.99 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.84, 16.94, 22,01, 28.83, 36.23, 37.74, 40.51, 73.34, 126.65, 135.08. Found: C, 77.65; H, 11.99%. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76%.

1- *tert*–Butyl–3–cyclohexen–1–ol (1c)



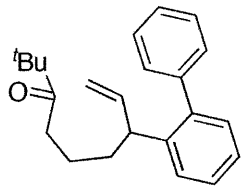
IR (neat) 3479, 2961, 1367, 1083, 872, 656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 9H), 1.46–1.52 (m, 2H), 1.74–1.79 (m, 1H), 1.91–1.97 (m, 1H), 2.03–2.11 (m, 1H), 2.14–2.24 (m, 1H), 2.26–2.32 (m, 1H), 5.59–5.63 (m, 1H), 5.74–5.78 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.35, 25.01, 27.04, 32.92, 37.36, 73.84, 124.94, 126.94. Found: C, 77.76; H, 12.01%. Calcd for $C_{10}H_{18}O$: C, 77.84; H, 11.76%.

7–(2,6–Dimethylphenyl)–2,2–dimethyl–8–nonen–3–one (3a)



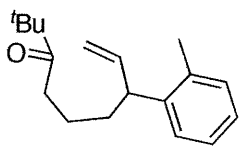
IR (neat) 2931, 2869, 1706, 1633, 1467, 1366, 992, 912, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9H), 1.37–1.46 (m, 1H), 1.58–1.67 (m, 1H), 1.73–1.90 (m, 2H), 2.40 (s, 6H), 2.46 (dt, J = 2.5, 7.5 Hz, 2H), 3.81–3.86 (m, 1H), 4.94 (ddd, J = 17.5, 2.0, 2.0 Hz, 1H), 5.04 (ddd, J = 10.0, 2.0, 2.0 Hz, 1H), 6.09 (ddd, J = 17.5, 10.0, 5.0 Hz, 1H), 6.75–7.05 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.73, 22.73, 26.51, 32.45, 36.50, 44.13, 44.21, 114.05, 126.09, 129(br), 136.71, 140.09, 140.57, 215.80. Found: C, 84.05; H, 10.34%. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36%.

2,2–Dimethyl–7–(2–phenylphenyl)–8–nonen–3–one (3b)



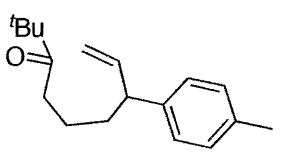
IR (neat) 2933, 1706, 1478, 1367 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.29–1.36 (m, 2H), 1.58–1.63 (m, 2H), 2.25 (dd, J = 14.0, 6.5 Hz, 2H), 3.44 (q, J = 7.5 Hz, 1H), 4.83–5.01 (m, 2H), 5.92–5.99 (m, 1H), 7.20–7.42 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 21.55, 26.53, 35.54, 36.12, 44.13, 44.45, 114.33, 125.86, 127.02, 127.13, 127.83, 128.16, 129.61, 130.18, 141.46, 141.89, 142.24, 142.75, 215.98. Found: C, 86.29; H, 8.93%. Calcd for $C_{23}H_{28}O$: C, 86.20; H, 8.81%.

2,2–Dimethyl–7–(2–methylphenyl)–8–nonen–3–one (3c)



IR (neat) 2955, 1706, 1478, 1367 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 9H), 1.44–1.54 (m, 1H), 1.58–1.74 (m, 3H), 2.33 (s, 3H), 2.48 (t, J = 7.0 Hz, 2H), 3.50 (t, J = 7.0 Hz, 1H), 4.96–5.02 (m, 2H), 5.85–5.91 (m, 1H), 7.07–7.18 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.81, 22.19, 26.58, 34.69, 36.50, 44.22, 45.21, 114.35, 126.05, 126.34, 126.43, 130.54, 135.97, 141.73, 142.31, 216.00. Found: C, 83.64; H, 10.14%. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14%.

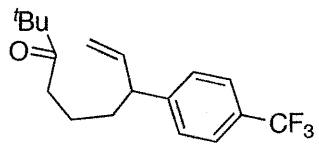
2,2–Dimethyl–7–(4–methylphenyl)–8–nonen–3–one (3d)



IR (neat) 2925, 1706, 1513, 1464, 1367, 816 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 9H), 1.41–1.51 (m, 1H), 1.54–1.71 (m, 3H), 2.31 (s, 3H), 2.46 (t, J = 6.5 Hz, 2H), 3.20 (q, J = 2.5 Hz, 1H), 4.99–5.04 (m, 2H), 5.89–5.96 (m, 1H), 7.06–7.12 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.18, 22.12, 26.58, 35.12, 36.41, 44.23, 49.69, 114.13, 127.57, 129.33, 135.84, 141.38, 142.43, 216.01.

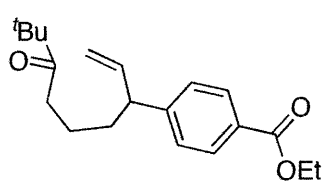
Found: C, 83.77; H, 9.84%. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14%.

2,2–Dimethyl–7–(4–trifluoromethylphenyl)–8–nonen–3–one (3e)



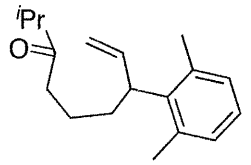
IR (neat) 2969, 1706, 1618, 1326, 1164, 1124, 1070, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.32–1.67 (m, 4H), 2.40 (t, J = 6.8 Hz, 2H), 3.24 (q, J = 7.5 Hz, 1H), 4.69–5.01 (m, 2H), 5.84 (ddd, J = 17.5, 10.0, 7.5 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.99, 26.57, 34.94, 36.28, 44.24, 50.01, 115.25, 124.45 (q, J = 271 Hz), 125.60 (q, J = 4 Hz), 128.10, 128.69 (q, J = 32 Hz), 141.23, 148.47, 215.83. Found: C, 69.00; H, 7.37%. Calcd for $C_{18}H_{23}F_3O$: C, 69.21; H, 7,42; F, 18.25%.

7–(4–Ethoxycarbonylphenyl)–2,2–dimethyl–8–nonen–3–one (3f)



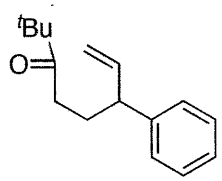
IR (neat) 2971, 1717, 1610, 1277, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.31 (t, J = 7.5 Hz, 3H), 1.32–1.40 (m, 1H), 1.43–1.69 (m, 3H), 2.40 (t, J = 7.5 Hz, 2H), 3.23 (q, J = 7.5 Hz, 1H), 4.29 (q, J = 7.5 Hz, 2H), 4.95–4.99 (m, 2H), 5.82–5.89 (m, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.52, 22.01, 26.55, 24.95, 36.28, 44.21, 50.13, 60.96, 115.09, 127.73, 128.68, 129.97, 141.31, 149.69, 166.74, 215.81. Found: C, 75.90; H, 8.87%. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%.

7–(2,6–Dimethylphenyl)–2–methyl–8–nonen–3–one (3g)



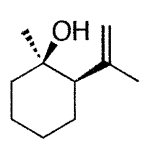
IR (neat) 2968, 2360, 1714, 1468, 993, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, J = 7.0 Hz, 6H), 1.38–1.46 (m, 1H), 1.57–1.67 (m, 1H), 1.73–1.81 (m, 1H), 1.83–1.90 (m, 1H), 2.33 (s, 6H), 2.43 (t, J = 7.0 Hz, 2H), 2.55 (sept, J = 7.0 Hz, 1H), 3.80–3.85 (m, 1H), 4.93 (ddd, J = 17.0, 2.0, 1.5 Hz, 1H), 5.03 (ddd, J = 10.5, 2.0, 1.5 Hz, 1H), 6.07 (ddd, J = 17.0, 10.5, 5.0 Hz, 1H), 6.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 18.42, 21.79, 22.66, 32.50, 40.44, 40.95, 44.21, 114.19, 126.16, 129 (br), 136.79, 140.13, 140.56, 214.83. Found: C, 83.63; H, 9.95%. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14%.

2,2–Dimethyl–6–(1–naphthyl)–7–octen–3–one (3h)



IR (neat) 2967, 1703, 1477, 1367, 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 2.08–2.23 (m, 2H), 2.50–2.58 (m, 2H), 4.16 (q, J = 7.5 Hz, 1H), 5.10–5.13 (m, 2H), 6.03–6.10 (m, 1H), 7.39 (dd, J = 7.5, 1.5 Hz, 1H), 7.44–7.55 (m, 3H), 7.73 (d, J = 8.0 Hz, 1H), 7.86 (dd, J = 8.0, 1.5 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.62, 29.14, 34.49, 43.52, 44.28, 115.27, 123.65, 124.10, 125.59, 125.69, 126.05, 127.08, 129.05, 131.94, 134.22, 140.00, 141.57, 215.97. Found: C, 85.60; H, 8.46%. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63%.

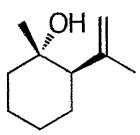
***erythro*–1–Methyl–2–(1–methylethenyl)–1–cyclohexanol (*erythro*–4a)**



IR (neat) 3494, 2931, 1638, 1449, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.16–1.25 (m,

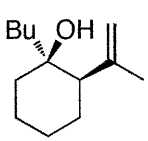
1H), 1.29–1.36 (m, 1H), 1.39–1.44 (m, 1H), 1.47–1.75 (m, 6H), 1.80 (s, 3H), 1.89 (dd, J = 13.0, 3.5 Hz, 1H), 4.74 (s, 1H), 4.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.91, 24.86, 26.38, 27.97, 30.10, 40.16, 53.62, 70.54, 112.00, 148.65. HRMS (EI) Found: 154.1360 [M^+]; Calcd for $C_{10}H_{18}O$: 154.1358.

threo–1–Methyl–2–(1–methylethenyl)–1–cyclohexanol (_threo_–4a)



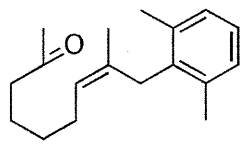
IR (neat) 3426, 2933, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.21–1.36 (m, 2H), 1.39–1.47 (m, 2H), 1.61–1.75 (m, 4H), 1.77 (s, 3H), 2.01 (bs, 1H), 2.12 (dd, J = 12.5, 3.5 Hz, 1H), 4.75–4.76 (m, 1H), 4.93–4.95 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.47, 22.91, 24.10, 26.26, 28.74, 41.74, 55.23, 72.29, 114.11, 146.56. HRMS (CI) Found: 154.1357 [M^+]; Calcd for $C_{10}H_{18}O$: 154.1358.

erythro–1–Butyl–2–(1–methylethenyl)–1–cyclohexanol (_erythro_–4c)



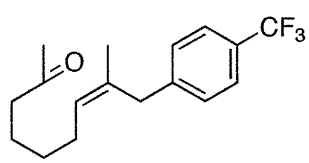
IR (neat) 3497, 2934, 1637, 1448, 889 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3H), 1.19–1.33 (m, 6H), 1.37–1.45 (m, 4H), 1.53–1.61 (m, 2H), 1.67–1.76 (m, 3H), 1.80 (s, 3H), 1.99 (dd, J = 13.0, 4.0 Hz, 1H), 4.76 (bs, 1H), 4.85 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.30, 21.76, 23.54, 24.46, 25.95, 26.43, 28.33, 36.32, 42.02, 52.38, 72.79, 112.18, 148.70. Found: C, 79.39; H, 12.49%. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32%.

(_Z_)–9–(2,6–Dimethylphenyl)–8–methyl–7–nonen–2–one ((_Z_)–5a)



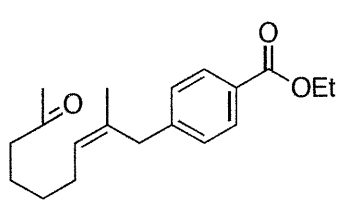
IR (neat) 2933, 1717, 1436, 1360, 1163, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.37–1.43 (m, 2H), 1.60–1.66 (m, 2H), 2.15 (q, J = 7.0 Hz, 2H), 2.16 (s, 3H), 2.28 (s, 6H), 2.46 (t, J = 7.5 Hz, 2H), 3.43 (s, 2H), 5.21–5.24 (m, 1H), 6.98–7.03 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 20.54, 22.54, 23.81, 27.80, 29.42, 30.08, 31.73, 43.87, 125.75, 125.92, 128.13, 133.07, 137.06, 137.18, 209.41. Found: C, 83.38; H, 10.34%. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14%.

(Z)–8–Methyl–9–(4–trifluoromethylphenyl)–7–nonen–2–one ((Z)–5b)



IR (neat) 2392, 1717, 1327, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36–1.42 (m, 2H), 1.60 (s, 3H), 1.58–1.65 (m, 2H), 2.12 (q, J = 7.0 Hz, 2H), 2.13 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H), 3.40 (s, 2H), 5.32–5.35 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 23.49, 23.66, 28.16, 29.62, 30.08, 37.82, 43.77, 123.52 (q, J = 270 Hz), 125.41 (q, J = 4 Hz), 127.31, 128.34 (q, J = 32 Hz), 128.92, 133.25, 144.50, 209.24. Found: C, 68.56; H, 7.05%. Calcd for $C_{17}H_{21}F_3O$: C, 68.44; H, 7.09%.

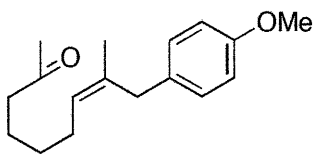
(Z)–9–(4–Ethoxycarbonylphenyl)–8–methyl–7–nonen–2–one ((Z)–5c)



IR (neat) 1717, 1611, 1276, 1103 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3H), 1.35–1.41 (m, 2H), 1.59 (s, 3H), 1.57–1.63 (m, 2H), 2.12 (q, J = 7.0 Hz, 2H), 2.13 (s, 3H), 2.43 (t, J = 7.0 Hz, 2H), 3.40 (s, 2H), 4.35 (q, J = 7.0 Hz, 2H), 5.30–5.33 (m, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.95

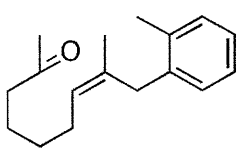
(d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.51, 23.52, 23.66, 28.15, 29.62, 30.08, 38.04, 43.78, 60.94, 127.11, 128.39, 128.62, 129.80, 133.43, 145.82, 166.82, 209.29. Found: C, 75.34; H, 8.86%. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67%.

(Z)–9–(4–Methoxyphenyl)–8–methyl–7–nonen–2–one ((Z)–5d)



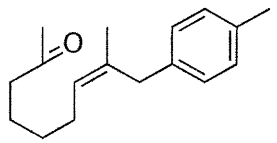
IR (neat) 2933, 1717, 1510, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35–1.41 (m, 2H), 1.60 (s, 3H), 1.58–1.64 (m, 2H), 2.13 (s, 3H), 2.11–2.16 (m, 2H), 2.43 (t, J = 7.5 Hz, 2H), 3.29 (s, 2H), 3.78 (s, 3H), 5.25–5.28 (m, 1H), 6.82 (d, J = 9.0 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 23.49, 23.71, 28.04, 29.74, 30.08, 37.04, 43.84, 55.41, 113.87, 126.10, 129.53, 132.33, 134.68, 157.95, 209.41. Found: C, 78.50; H, 9.38%. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29%.

(Z)–8–Methyl–9–(2–methylphenyl)–7–nonen–2–one ((Z)–5e)



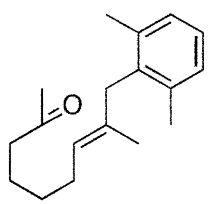
IR (neat) 2932, 1717, 1358 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36–1.42 (m, 2H), 1.60 (s, 3H), 1.58–1.64 (m, 2H), 2.08 (q, J = 7.5 Hz, 2H), 2.13 (s, 3H), 2.29 (s, 3H), 2.42 (t, J = 7.5 Hz, 2H), 3.33 (s, 2H), 5.34 (dt, J = 1.0, 7.0 Hz, 1H), 7.08–7.15 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.78, 23.70, 23.74, 27.98, 29.54, 30.04, 35.28, 43.81, 126.01, 126.05, 126.81, 128.46, 130.08, 133.46, 136.71, 138.09, 209.40. Found: C, 83.83; H, 10.01%. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90%.

(Z)–8–Methyl–9–(4–methylphenyl)–7–nonen–2–one ((Z)–5f)



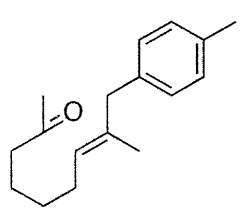
IR (neat) 2927, 1717, 1513, 1456, 1363, 1261, 1163, 1022, 795 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36–1.42 (m, 2H), 1.61 (s, 3H), 1.59–1.65 (m, 2H), 2.14 (s, 3H), 2.16 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 2.44 (t, J = 7.5 Hz, 2H), 3.32 (s, 2H), 5.26–5.29 (m, 1H), 7.05 (d, J = 7.0 Hz, 2H), 7.09 (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.15, 23.52, 23.69, 28.04, 29.70, 30.04, 37.51, 43.82, 126.21, 128.50, 129.15, 134.47, 135.42, 137.17, 209.36. HRMS (EI) Found: 244.1827 [M^+]; Calcd for $C_{17}H_{24}O$: 244.1827.

(*E*)–9–(2,6–Dimethylphenyl)–8–methyl–7–nonen–2–one ((*E*)–5a)



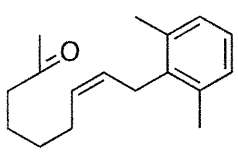
IR (neat) 2930, 1717, 1358, 1163, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (quintet, J = 7.5 Hz, 2H), 1.50 (quintet, J = 7.5 Hz, 2H), 1.69 (s, 3H), 1.96 (q, J = 7.5 Hz, 2H), 2.11 (s, 3H), 2.23 (s, 6H), 2.37 (t, J = 7.5 Hz, 2H), 3.27 (s, 2H), 4.63 (dt, J = 1.5, 7.5 Hz, 1H), 6.99–7.05 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 17.42, 20.03, 23.62, 27.73, 29.38, 29.95, 38.64, 43.82, 123.35, 125.95, 127.91, 132.47, 136.77, 137.32, 207.45. HRMS (EI) Found: 258.1982 [M^+]; Calcd for $C_{18}H_{26}O$: 258.1984.

(*E*)–8–Methyl–9–(4–methylphenyl)–7–nonen–2–one ((*E*)–5f)



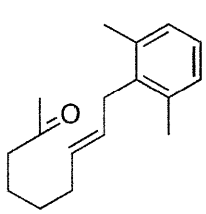
IR (neat) 2927, 1718, 1512, 1360, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (quintet, J = 7.5 Hz, 2H), 1.53 (s, 3H), 1.60 (quintet, J = 7.5 Hz, 2H), 2.03 (q, J = 7.5 Hz, 2H), 2.14 (s, 3H), 2.32 (s, 3H), 2.43 (t, J = 7.5 Hz, 2H), 3.24 (s, 2H), 5.23 (dt, J = 1.5, 7.5 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.95, 21.18, 23.67, 27.90, 29.44, 30.02, 43.85, 45.95, 126.08, 128.82, 129.04, 135.07, 135.48, 137.44, 209.47. Found: C, 83.65; H, 10.04%. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90%.

(Z)–9–(2,6–Dimethylphenyl)–7–nonen–2–one ((Z)–5g)



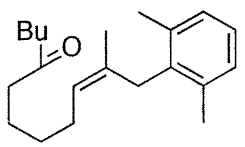
IR (neat) 2933, 1718, 1359, 1162, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.46 (m, 2H), 1.63–1.69 (m, 2H), 2.16 (s, 3H), 2.19–2.24 (m, 2H), 2.30 (s, 6H), 2.47 (t, J = 7.5 Hz, 2H), 3.37 (dd, J = 6.5, 1.5 Hz, 2H), 5.21–5.27 (m, 1H), 5.37–5.43 (m, 1H), 7.01 (brs, 3H); ^{13}C NMR ($CDCl_3$) δ 20.18, 23.78, 27.51, 28.22, 29.32, 30.04, 43.82, 126.01, 127.55, 128.24, 129.94, 136.45, 138.03, 209.10. Found: C, 83.45; H, 10.02%. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90%.

(*E*)–9–(2,6–Dimethylphenyl)–7–nonen–2–one ((*E*)–5g)



IR (neat) 2933, 1718, 1452, 1359, 968, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28–1.34 (m, 2H), 1.50–1.56 (m, 2H), 1.95–2.00 (m, 2H), 2.11 (s, 3H), 2.29 (s, 6H), 2.39 (t, J = 7.5 Hz, 2H), 3.32 (dd, J = 5.5, 1.0 Hz, 2H), 5.23–5.30 (m, 1H), 5.44–5.49 (m, 1H), 6.99–7.03 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 20.02, 23.53, 29.16, 29.95, 32.41, 32.72, 43.78, 126.02, 127.19, 128.15, 130.49, 136.68, 137.18, 209.23. Found: C, 83.48; H, 10.00%. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90%.

(*Z*)–11–Methyl–12–(2,6–dimethylphenyl)–10–dodecen–5–one ((*Z*)–5h)



IR (neat) 2933, 1715, 1468, 1377, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 3H), 1.32 (q, J = 7.5 Hz, 2H), 1.36–1.43 (m, 2H), 1.40 (s, 3H), 1.54–1.60 (m, 2H), 1.60–1.66 (m, 2H), 2.14 (q, J = 7.0 Hz, 2H), 2.28 (s, 6H), 2.42 (q, J = 7.5 Hz, 4H), 3.43 (s, 2H), 5.21–5.24 (m, 1H), 6.98–7.03 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.03, 20.51, 22.52, 22.56, 23.86, 26.16, 27.83, 29.53, 31.74, 42.72, 42.89, 125.82, 125.93, 128.13, 133.05, 137.08, 137.19, 211.62. Found: C, 83.74; H, 10.39%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

References and Notes

1. (a) Necas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566–1591. (b) Jun, C.–H. *Chem. Soc. Rev.* **2004**, *33*, 610–618. (c) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315–1321. (d) Kondo, T.; Mitsudo, T. *Chem. Lett.* **2005**, *34*, 1462–1467.
2. (a) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010–11011. (b) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645.
3. Murakami, M.; Amii, H.; Shigeto, K.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8285–8290.
4. Necas, D.; Kotora, M. *Org. Lett.* **2008**, *10*, 5261–5263.
5. Sumida, Y.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2010**, *12*, 2254–2257.
6. Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211.
7. For the *erythro/threo* nomenclature, see: Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106–2108.
8. Konakahara, T.; Takaji, Y. *Synthesis* **1979**, 192–194.

Chapter 2

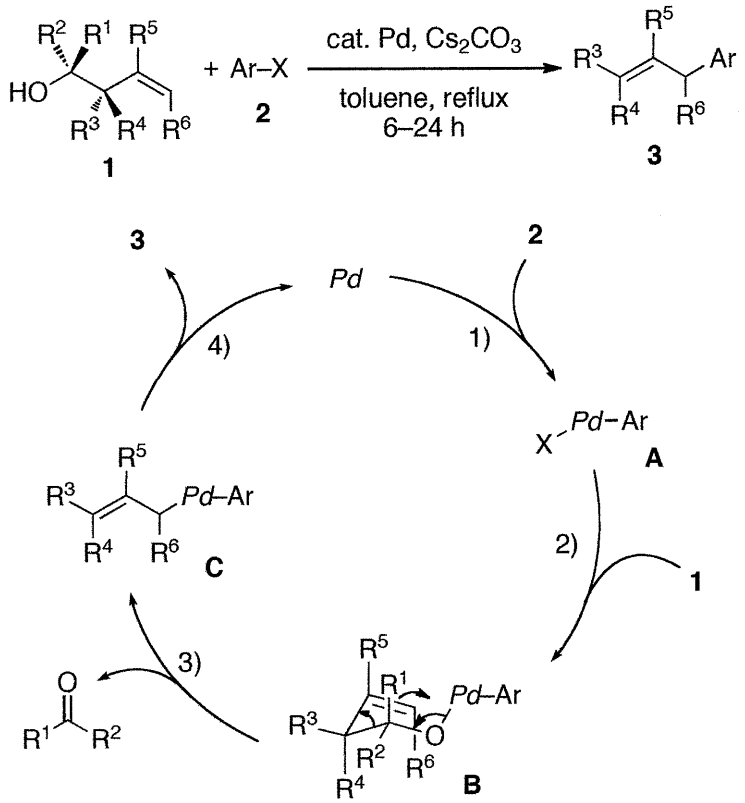
Microwave–Assisted Palladium–Catalyzed Allylation of Aryl Halides with Homoallyl Alcohols via Retro–Allylation

The palladium–catalyzed allylation of aryl halides with homoallyl alcohols via retro–allylation proceeds at 200–250 °C in a toluene–DMF mixed solvent using microwave heating. Even at such high temperatures, the regio– and stereospecificity of the allyl transfer reaction are still satisfactory. The amount of the palladium catalyst can be reduced to 0.5 or 0.05 mol%.

Introduction

The use of homoallyl alcohols as the allyl sources in the palladium–catalyzed allylations of organic halides instead of allylmetal reagents is reported (Scheme 1).[1] In Chapter 1, the author described arylative ring opening reaction of cyclic homoallyl alcohols with aryl bromides under palladium catalysis. These allylation reactions would proceed as follows: 1) oxidative addition of aryl halide **2**, 2) ligand exchange with homoallyl alcohol **1** to afford alkoxy(aryl)palladium **B**, 3) retro–allylation reaction of **B** providing σ–allyl(aryl)palladium **C**, and 4) reductive elimination to yield **3**. The reaction provides a variety of allylated arenes in regio– and stereospecific manners and are thus useful in organic synthesis. However, the allylation of aryl halides in refluxing toluene required prolonged reaction time, *ca.* 6–24 h. Shorter reaction time is preferable to improve the productivity of the reaction and to enable high–throughput screenings. In Chapter 2, the author reports the microwave–assisted allylation reactions of aryl halides with homoallyl alcohols, which proceed to completion within 15 min in most cases.[2,3]

Scheme 1.

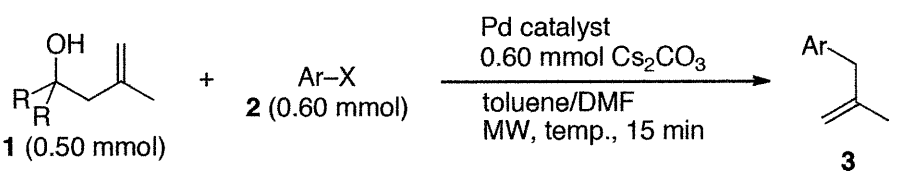


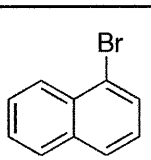
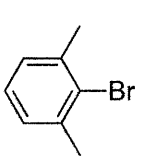
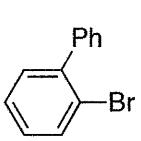
Results and Discussion

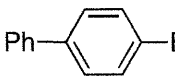
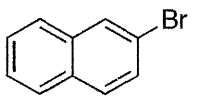
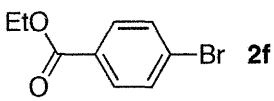
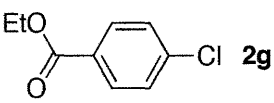
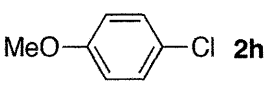
Treatment of 1–bromonaphthalene (**2a**) with homoallyl alcohol **1a** in the presence of cesium carbonate at 200 °C for 15 min under microwave irradiation and palladium catalysis provided 1–methallylnaphthalene (**3a**) in excellent yield (Table 1, entry 1). Instead of toluene alone,[1] a toluene–DMF mixed solvent was used to improve the efficiency of microwave heating. Not only diisopropyl–substituted **1a** but also dimethyl–substituted **1b** participated in the methallyl transfer reaction (entry 2). Aryl bromides having substituents at the *ortho* positions were smoothly methallylated to yield the corresponding products in high yields (entries 3 and 4). The yields were comparable to those previously reported for the reaction in toluene at 110 °C.[1a] When the reactions were performed at 250 °C, the amount of the palladium catalyst could be reduced from 5 mol% of $Pd(OAc)_2$ and 20 mol% of P(*p*–tol)$_3$ to 0.5 mol% and 2 mol%,

respectively (entries 5 and 6). The reaction of 4–bromobiphenyl (**2d**), which has no substituent at the *ortho* position, resulted in a moderate yield of the methallylated product (entry 7). To improve the yield of **3d**, tricyclohexylphosphine (PCy_3) was a useful ligand (entry 8).[1b] PCy_3 also allowed for the use of aryl chlorides as substrates (entries 11–14). Electron–rich as well as electron–deficient aryl chlorides underwent the methallylation. It is worth noting that only 0.05 mol% of $Pd(OAc)_2$ functioned to catalyze the reaction wherein the turnover number was 1.6×10^3 (entry 13). The best $Pd(OAc)_2/PCy_3$ ratio was 1:6 at 250 °C under microwave irradiation, whereas a $Pd(OAc)_2/PCy_3$ ratio of 1:2 was effective at 200 °C (entries 8 and 9) as well as in the previous report[1a] performed in refluxing toluene. When we used a 1:2 ratio at 250 °C under microwave irradiation, palladium black was likely to be generated during the heating. The palladium black would be heated extremely by microwaves, causing the reaction vial to shatter.[4]

Table 1. Allylation of Aryl Halides with Homoallyl Alcohols under Microwave Irradiation



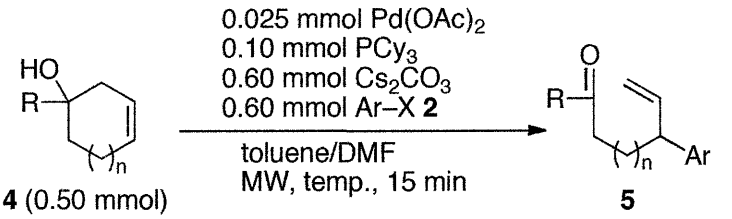
entry	**1**[a]	**2**	$Pd(OAc)_2$ (mmol)	ligand, mmol	temp[b] (°C)	**3**, yield[c] (%)
1	**1a**	 **2a**	0.025	P(*p*–tol)$_3$, 0.10	200	**3a**, 90 (86)
2	**1b**	**2a**	0.025	P(*p*–tol)$_3$, 0.10	200	**3a**, 94
3	**1a**	 **2b**	0.025	P(*p*–tol)$_3$, 0.10	200	**3b**, 87 (90)
4	**1a**	 **2c**	0.025	P(*p*–tol)$_3$, 0.10	200	**3c**, 100 (91)

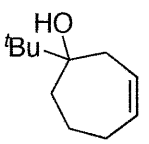
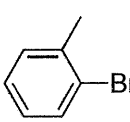
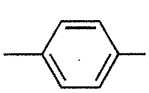
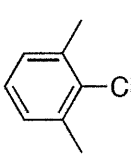
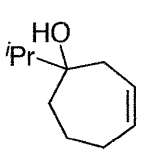
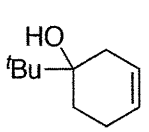
5	**1a**	**2b**	0.0025	P(*p*–tol)$_3$, 0.010	250	**3b**, 62
6	**1a**	**2c**	0.0025	P(*p*–tol)$_3$, 0.010	250	**3c**, 95
7	**1a**	 **2d**	0.025	P(*p*–tol)$_3$, 0.10	200	**3d**, 41 (34)
8	**1a**	**2d**	0.025	PCy_3, 0.050	200	**3d**, 61 (83)
9	**1a**	 **2e**	0.025	PCy_3, 0.050	200	**3e**, 53 (86)
10	**1b**	 **2f**	0.025	PCy_3, 0.15	250	**3f**, 97[d]
11	**1a**	 **2g**	0.025	PCy_3, 0.050	200	**3f**, 72 (79)
12	**1a**	**2g**	0.0025	PCy_3, 0.015	250	**3f**, 86
13	**1a**	**2g**	0.00025	PCy_3, 0.0015	250	**3f**, 78
14	**1a**	 **2h**	0.025	PCy_3, 0.15	250	**3g**, 98 (70)

[a] **1a**: R = ^{i}Pr, **1b**: R = Me. [b] The reactions at 200 °C were performed in a mixed solvent of toluene (2.0 mL) and DMF (0.20 mL). The reactions at 250 °C were performed in toluene (2.0 mL) and DMF (0.40 mL) to improve the efficiency of microwave heating further. [c] The yields reported in the literature[1] by performing the reactions in refluxing toluene for 8 h are in parentheses. [d] Performed for 20 min.

Microwave heating was applicable to the arylative ring–opening reactions of endocyclic homoallyl alcohols (Table 2).[1b] In most cases, the yields were higher than those obtained by the conventional heating at 140 °C (Chapter 1). The reactions of aryl halides having *ortho* substituents proceeded at 200 °C (entries 1–3, 5). The reaction of *p*–bromotoluene (**2j**) required heating at 250 °C to attain satisfactory yield (entry 4). Unfortunately, the reactions of **4b** and **4c** at 250 °C were still unsatisfactory by using microwave heating.

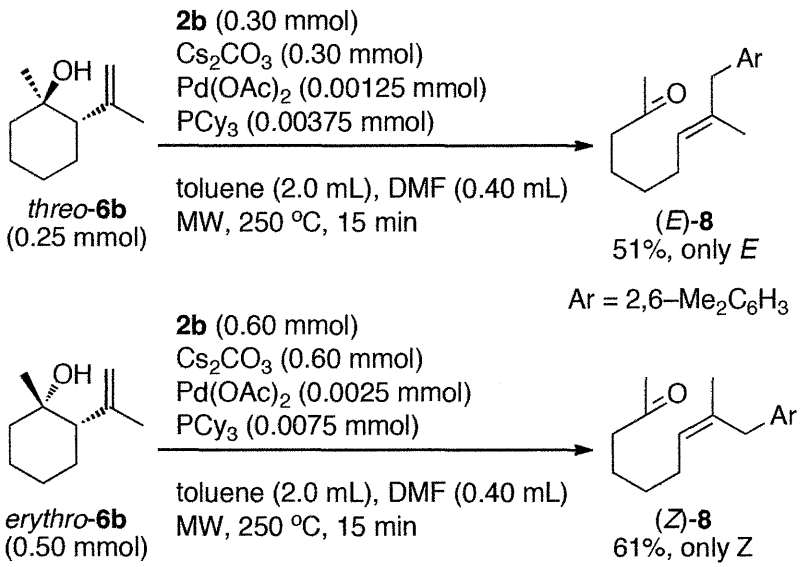
Table 2. Arylative Ring–opening Reaction Using Microwave Heating



entry	4	2	temp[a] (°C)	yield[b] (%)
1	 **4a**	**2b**	200	**5a**, 88 (80)
2	**4a**	**2c**	200	**5b**, 76 (68)
3	**4a**	 **2i**	200	**5a**, 94 (70)
4[c]	**4a**	 **2j**	250	**5d**, 75 (65)
5	**4a**	 **2k**	200	**5a**, 83
6	 **4b**	**2b**	250	**5e**, 36 (20)
7[d]	 **4c**	**2b**	250	**5f**, 47 (59)

[a] The reactions at 200 °C were performed in a mixed solvent of toluene (2.0 mL) and DMF (0.20 mL). The reactions at 250 °C were performed in toluene (2.0 mL) and DMF (0.40 mL). [b] The yields reported in the literature[1b] by performing the reactions in refluxing xylene for 12 or 24 h are in parentheses. [c] 0.15 mmol of PCy_3 was used. [d] 0.050 mmol of PCy_3 was used.

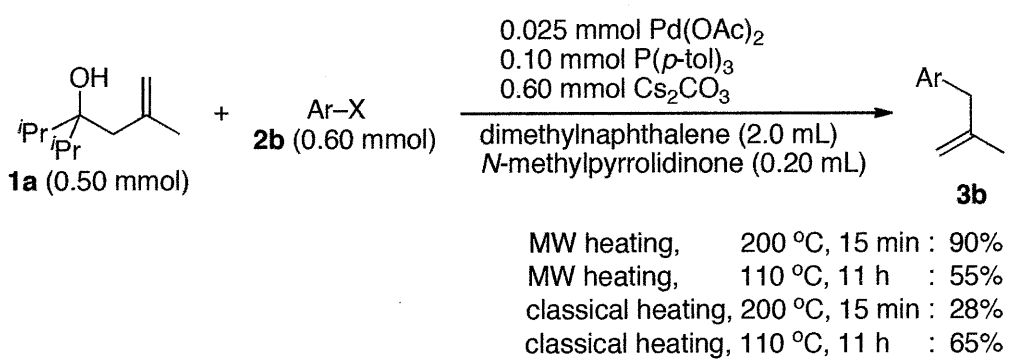
Treatment of **2a** with *threo*–**6a** in the presence of 0.5 mol% of palladium acetate and 1.0 mol% of PCy_3 at 250 °C afforded (*E*)–1–crotylnaphthalene (*E*)–**7** stereoselectively (Scheme 2). Similar treatment with *erythro*–**6a** afforded (*Z*)–**7** exclusively. Stereospecificity was thus observed even at 250 °C. Stereospecificity was also observed in the reactions of alkenylcyclohexanol *threo*– and *erythro*–**6b**.



It was reported that microwave heating is not only a simple heating method but also can have so–called *nonthermal microwave effects*.[2,5] If there are any nonthermal microwave effects, the followings may be included: (1) microwave-assisted activation of the polar transition state of the retro–allylation step, (2) preventing the formation of palladium black, and (3) intervention of localized microscopic high temperatures. Very recently, Kappe disclosed the method to rapidly evaluate whether an observed enhancement seen in a microwave-assisted chemical transformation is the result of a purely thermal phenomenon, or whether specific/nonthermal microwave effects are involved.[6] He demonstrated some microwave–assisted reactions by making use of his method and thus found nonthermal microwave effects were not observed in those reactions.

In order to confirm nonthermal microwave effects in palladium–catalyzed rerto–allylation reaction, the experiments shown in Scheme 3 were performed. As a result, the reaction of **1a** with **2b** completed smoothly within 15 min in a dimethylnaphthalene (bp: ca. 260 °C)/*N*–methylpyrrolidinone (bp: 202 °C) mixed solvent by using microwave heating at 200 °C, whereas the same reaction was sluggish by classical heating for 15 min at 200 °C. Although this seems to be the case for nonthermal microwave effects, considering the result by Kappe, the author can not explain whether nonthermal microwave effects operated so far. The author is afraid that the reaction mixture actually reached 200 °C with classical heating. As shown in Scheme 3, the reaction did actually proceed albeit in moderate yield when heating the reaction mixture at 110 °C for 11 h without microwave heating.

Scheme 3.



Needless to say, it is not easy to perform allylation reactions at the temperature above 200 °C with classical equipments such as oil baths and sand baths. At least, microwave reactors, however, could allow us to perform the reaction at extremely high temperature easily and safely and are hence useful in the system even without nonthermal microwave effects.

Conclusion

Microwave heating promotes the palladium–catalyzed allylation of aryl halides with

homoallyl alcohols. The microwave heating easily allowed us to perform the reactions at 200–250 °C. Even at such high temperatures, the regio– and stereospecificity of the allyl transfer reaction are excellent. In addition, the amount of the palladium catalyst can be reduced to 0.5 or 0.05 mol%.

Experimental Section

Instrumentation

Unless otherwise noted, all the reactions were carried out using a focused microwave unit (Biotage Initiator™). The maximum irradiation power is 400 W. Each reaction was run in a 5–mL glass pressure vial, which is a commercially available vial special for the Biotage Initiator™. It took 2 min and 6 min to reach 200 °C and 250 °C, respectively. After reaching the indicated temperatures, controlled microwave irradiation started and continued for 15 min, keeping the reaction temperature constant. The classical heating at 200 °C or 110 °C shown in Scheme 3 was done in an oil bath.

^{1}H NMR (300 MHz and 500 MHz) and ^{13}C NMR (75.3 MHz and 125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.0 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR–8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25–mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Chemicals

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene, DMF, and *N*–methylpyrrolidinone were purchased from Wako Pure Chemical Co. Dimethylnaphthalene (mixture of regioisomers) were obtained from TCI. Toluene was stored over slices of sodium. Dimethylnaphthalene, DMF, and *N*–methylpyrrolidinone were used as received. Tri(*p*–tolyl)phosphine and cesium carbonate were purchased from Wako Pure Chemical Co. Palladium acetate and tricyclohexylphosphine were obtained from TCI and Acros, respectively. The homoallyl alcohols **1**, **4**, and **6** were

prepared according to the literature.[1b]

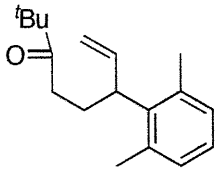
Typical Procedure

The reaction of entry 1 in Table 1 is representative. Cesium carbonate (0.20 g, 0.60 mmol), palladium acetate (5.6 mg, 0.025 mmol), and tri(*p*–tolyl)phosphine (30 mg, 0.10 mmol) were placed in a 5–mL glass pressure vial. The vial was flushed with argon and sealed with a PTFE–silicon septum. Toluene (2.0 mL) and DMF (0.20 mL) were added, and the mixture was stirred for 1 min. Homoallyl alcohol **1a** (85 mg, 0.50 mmol) and 1–bromonaphthalene (**2a**, 83 μL, 0.60 mmol) were added. The suspension was heated at 200 °C with stirring for 15 min in the microwave reactor. The mixture was then cooled to room temperature. Hydrochloric acid (1 M, 3 mL) was added. The organic layer formed was then washed with brine (5 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated. Silica gel column purification with hexane as an eluent afforded 1–methallylnaphthalene (**3a**, 82 mg, 0.45 mmol) in 90% yield.

Characterization Data

Spectral data for **3**, **5**, **7**, and **8** were found in the literature[1,7] except for **5f**.

2,2–Dimethyl–6–(2,6–dimethylphenyl)–7–octen–3–one (5f)



IR (neat) 2967, 1705, 1453, 1367, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H), 2.02–2.09 (m, 1H), 2.14–2.22 (m, 1H), 2.32 (s, 6H), 2.34–2.47 (m, 2H), 3.84–3.89 (m, 1H), 5.05 (dt, J = 10.5, 2.0 Hz, 2H), 6.08 (ddd, *J* = 17.5, 10.5, 5.5 Hz, 1H), 6.96–7.02 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.67, 26.54, 26.59, 34.54, 43.27, 44.25, 114.47, 126.28, 129 (brs), 136.95, 139.51, 140.29,

215.87. Found: C, 83.66; H, 10.09%. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14%.

References and Notes

1. (a) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211. (b) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4099–4104.
2. Reviews for microwave–assisted organic reactions: (a) *Microwave Assisted Organic Synthesis*, Tierney, J. P.; Lidström, P. Eds., Blackwell Publishing: Victoria, 2005. (b) *Microwave Methods in Organic Synthesis*, Larhed, M.; Olofsson, K., Springer–Verlag: Berlin, 2006. (c) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661. (d) Tokuyama, H.; Nakamura, M. *J. Synth. Org. Chem., Jpn.* **2005**, *63*, 523–538. (e) de la Hoz, A.; Diaz–Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178. (f) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284. (g) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283. (h) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432. (i) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1–47.
3. Microwave–assisted carbon–carbon bond cleavage has rarely been reported: (a) Tanner, D. D.; Kandanarachchi, P.; Ding, Q.; Shao, H.; Vizitiu, D.; Franz, J. A. *Energy Fuels* **2001**, *15*, 197–204. (b) Ahn, J.–A.; Chang, D.–H.; Park, Y. J.; Yon, Y. R.; Loupy, A.; Jun, C.–H. *Adv. Synth. Catal.* **2006**, *348*, 55–58.
4. **Caution:** The black precipitate resulted in extreme microwave absorption that caused reaction vial to shatter. Although the microwave reactor is explosion–proof, proper precautions should be taken.
5. (a) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136–9139. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223. (c) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863–1866. (d) Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589–3590.

6. Obermayer, D.; Gutmann, B.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321–8324.

7. For **3c**: Thatia, T.; Jayanth, T.; Jeganmohan, M.; Cheng, C.–H. *Org. Lett.* **2005**, *7*, 2921–2924.

Chapter 3

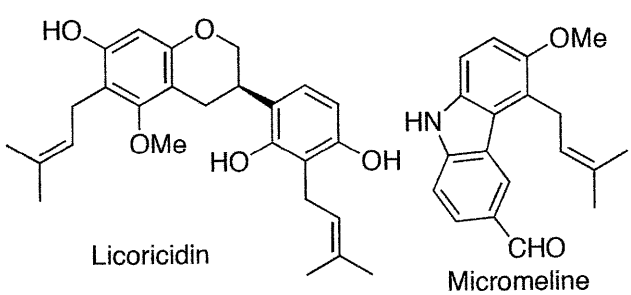
Synthesis of Prenylarenes and Related (Multisubstituted Allyl)arenes from Aryl Halides and Homoallyl Alcohols via Palladium–Catalyzed Retro–Allylation

The reactions of aryl halides with 2,3,3–trimethyl–4–penten–2–ol in the presence of a palladium catalyst result in prenyl transfer from the alcohol to aryl halides via retro–allylation, yielding prenylarenes. Other multisubstituted allyl groups such as a 2,3–dimethyl–2–butenyl group are introduced to aromatic rings.

Introduction

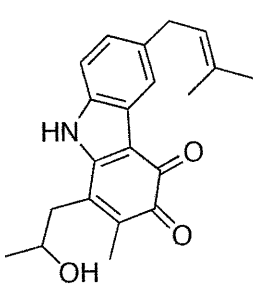
Prenyl–substituted arenes are often found in natural products, most of which show significant biological activities (Figure 1). The synthesis of such biologically interesting compounds has hence been well investigated.[1] However, construction of prenylarene skeletons is usually difficult. For instance, according to the report by Knölker about the synthesis of carquinostatin A,[2] the use of a large excess of nickel complex **1** was essential to afford **3** with satisfactory efficiency and selectivity (Scheme 1). Moreover, a large amount of highly toxic $Ni(CO)_4$ was required for the preparation of **1**, which can be a significant drawback. In most cases, the conventional cross–coupling reactions of aryl halides with prenylmetal reagents provide a mixture of regioisomers (eq 1).[3,4] Exceptionally, prenyltrifluorosilane reacted with aryl triflates under palladium catalysis to afford prenylarenes predominantly (eq 2).[4] However, the reactions were performed in sealed tubes and required the moisture–sensitive prenylmetal. Thus, little is known concerning regioselective and convenient prenylation reactions of aryl halides.

Figure 1. Some Natural Products Bearing Prenyl Groups

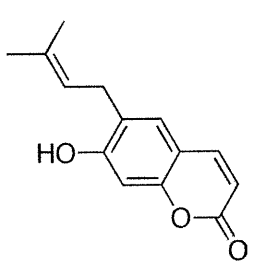


Licoricidin

Micromeline

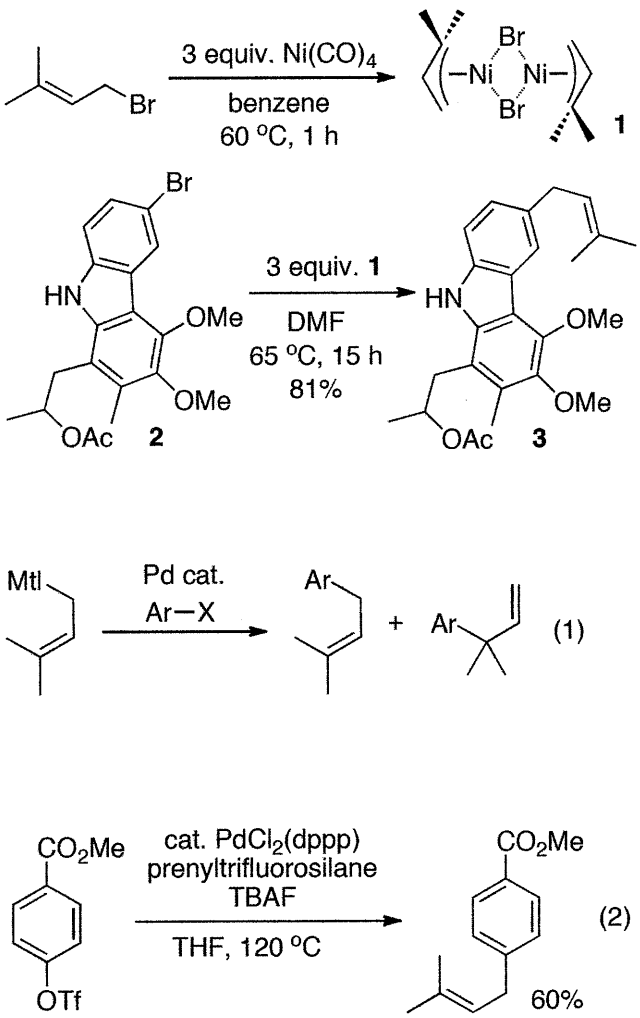


Carquinostatin A



Dimethylsuberosin

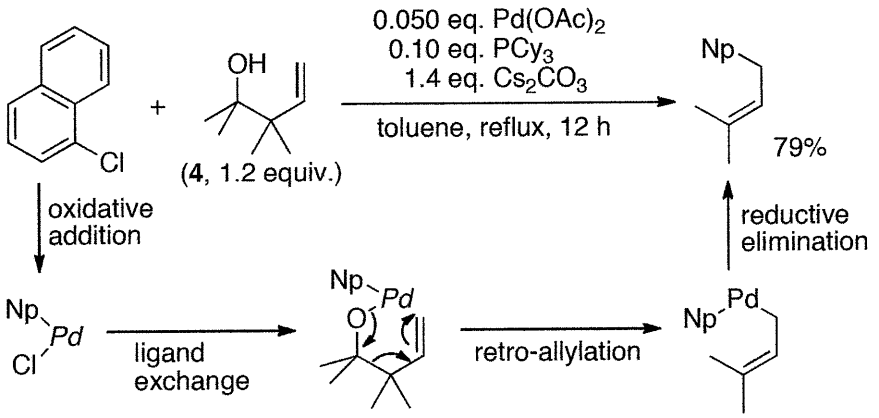
Scheme 1. A Rare Example of Selective Prenylation of Aryl Halide



Very recently, we have developed the palladium–catalyzed allylation reaction of aryl halides with homoallyl alcohols via palladium–catalyzed retro–allylation.[5] The reaction proceeds with high regiospecificity, providing a variety of allylated arenes. The prenylation of 1–bromonaphthalene with homoallyl alcohol **4** was previously investigated (Scheme 2).[5a,b] Notably, the prenylation reaction was perfectly regioselective, and none of the regioisomer was obtained.[5b] However, this is the only example of the prenylation reaction in the previous papers. In light of the importance of installing a prenyl moiety to aromatic compounds, the author further examined the generality of the prenylation reaction of aryl halides with **4**. In Chapter 3, the

author reports the details of the prenylation reaction and related reactions that introduce multisubstituted allyl groups into aryl halides.

Scheme 2.

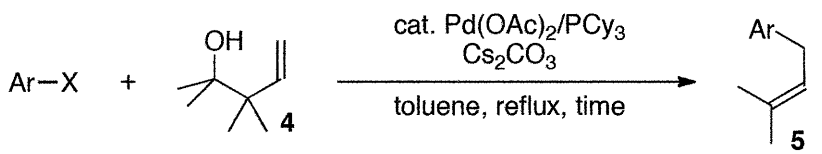


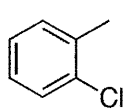
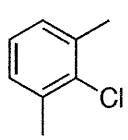
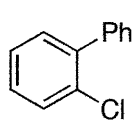
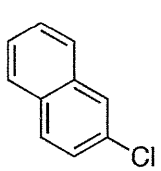
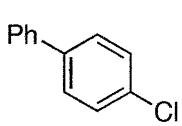
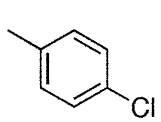
Results and Discussion

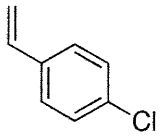
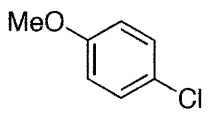
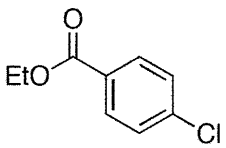
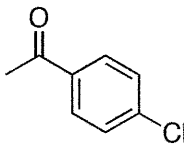
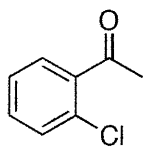
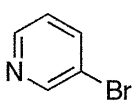
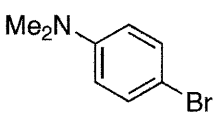
A variety of aryl halides were subjected to the palladium–catalyzed prenylation reaction with **4** (Table 1). Since highly electron–donating tricyclohexylphosphine was used as the ligand, aryl chlorides[6] were able to undergo the prenylation. The reactions of *ortho*–substituted chloroarenes proceeded with excellent efficiency (entries 1–3). On the other hand, the prenylation reactions of 2–chlorobiphenyl and 4–chlorotoluene were slow, and required 26 h to complete (entries 5 and 6). Although the reactions of 4–chlorostyrene and 4–chloroanisole were also inefficient at reflux in toluene, a higher temperature under microwave irradiation[7] could accelerate the reaction (entries 7 and 8). In the reactions of sterically demanding aryl chlorides (entries 1–3), the retro–allylation step would be accelerated by the steric repulsion around the palladium center. The high temperature could enhance the rate–determining retro–allylation step in the reactions in entries 7 and 8, where smaller steric repulsion would operate.[5c] Notably, none of the oligomers of 4–chlorostyrene, which could be formed through Mizoroki–Heck reaction,[8] were observed. The reaction conditions were mild enough to leave ester as well as

acetyl groups untouched (entries 9–11). Under the standard conditions, 3–bromopyridine resisted the reaction, and a high temperature was essential to attain a satisfactory result (entry 12). Both 3–chloropyridine and 2–bromopyridine suffered from very low conversions under several sets of reaction conditions we tested. Unprotected hydroxy and amino groups completely suppressed the reaction. A dimethylamino substituent also retarded the reaction (entry 13). Attempts to use 1–alkenyl halides resulted in very low yields.

Table 1. Palladium–Catalyzed Prenylation of Aryl Halides with Homoallyl Alcohol **4**[a]



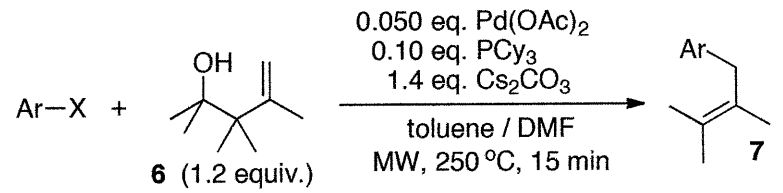
entry	Ar–X	time (h)	**5**	yield (%)
1		17	**5a**	100
2		10	**5b**	98
3		10	**5c**	86
4		15	**5d**	80
5		26	**5e**	93
6		26	**5f**	84[b]

7		11	**5g**	38 (84)[c)]
8		15	**5h**	27 (95)[c)]
9		15	**5i**	100
10		15	**5j**	80
11		10	**5k**	67
12		10	**5l**	< 5 (62)[c)]
13		17	**5m**	20

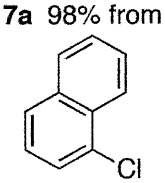
[a] Conditions: Ar–X (0.50 mmol), alcohol **4** (0.60 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.050 mmol), Cs_2CO_3 (0.70 mmol), and toluene (2 mL). [b] With $Pd(OAc)_2$ (0.050 mmol) and PCy_3 (0.10 mmol). [c] Performed under microwave irradiation at 250 °C for 15 min.

Not only the prenyl group but also a trisubstituted allyl group could be incorporated. The reactions of aryl halides with alcohol **6** provided 2,3–dimethyl–2–butenylarenes **7** through the transposition of the double bond (Scheme 3). The reactions are high–yielding under microwave irradiation at 250 °C, although the reaction of 1–chloronaphthalene with **6** in boiling toluene for 13 h resulted in low conversion, providing **7a** in only 31% yield. Preparation of such tetrasubstituted alkenes by conventional Wittig–type olefination often results in low yields.

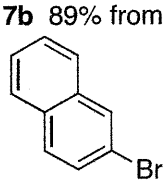
Scheme 3. Synthesis of 2,3–Dimethyl–2–butenylarenes



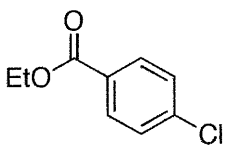
7a 98% from



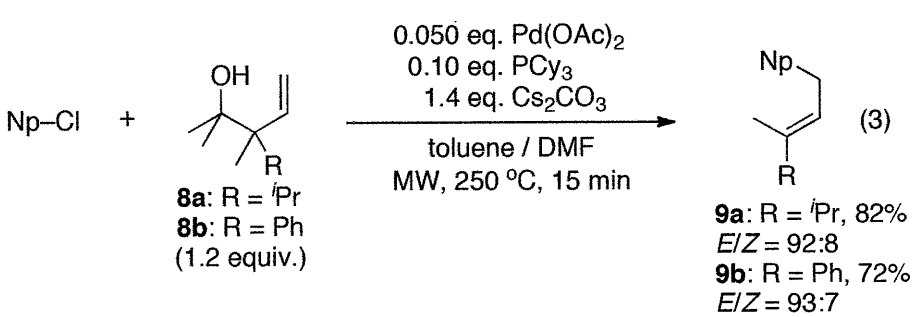
7b 89% from



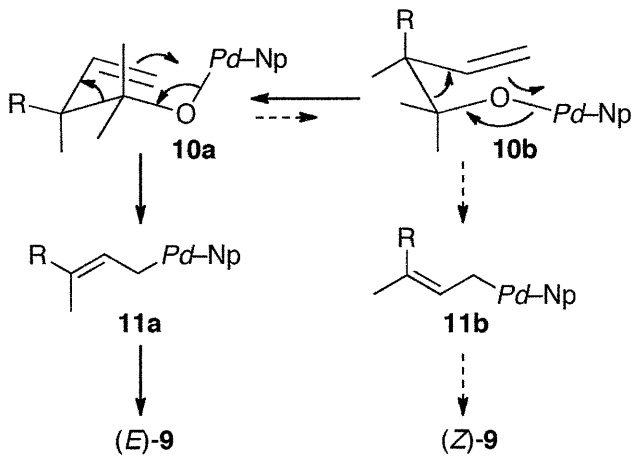
7c 89% from



Stereoselective synthesis of trisubstituted alkenes was performed by using **8**, which have two different substituents, methyl and the other bulkier groups at the allylic position (eq 3). Formation of the *E* isomers of **9** predominated, and the stereoselectivity can be rationalized as outlined in Scheme 4. Upon the retro–allylation reaction of **8**, a chairlike transition state **10a** would be the most favorable because the bulky R group is located at the equatorial position. The other chairlike transition state **10b** has the R group at the axial position, which would render **10b** disfavored. Formation of [(*E*)–alkenyl](naphthyl)palladium **11a** is thus preferred. The intermediate **11a** finally undergoes smooth reductive elimination to yield (*E*)–**9** selectively.



Scheme 4. Origin of Stereoselectivity



Conclusion

The author has disclosed the palladium–catalyzed prenylation and other related allylation of aryl halides that yield (multisubstituted allyl)arenes by using retro–allylation of homoallyl alcohols. The products are not readily available by conventional methods. The present reactions will find applications for the synthesis of biologically intriguing compounds.

Experimental Section

Instrumentation

^{1}H NMR (300 MHz and 500 MHz) and ^{13}C NMR (75.3 MHz and 125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.0 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR–8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25–mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

The reactions under microwave irradiation were carried out using a focused microwave unit (Biotage Initiator™). The maximum irradiation power is 400 W. Each reaction was run in a 5–mL glass pressure vial, which is a commercially available vial specifically for the Biotage Initiator™. It took 6 min to reach 250 °C. After reaching the indicated temperatures, controlled microwave irradiation started and continued for 15 min, keeping the reaction temperature constant.

Chemicals

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene and DMF were purchased from Wako Pure Chemical Co. Toluene was stored over slices of sodium. DMF was used as received. Tri(*p*–tolyl)phosphine and cesium carbonate were purchased from Wako Pure Chemical Co. Palladium acetate and tricyclohexylphosphine were obtained from TCI and Acros, respectively. The homoallyl alcohol **4** was prepared according to the literature.[5b]

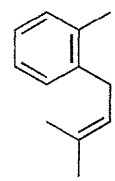
Typical Procedure (Table 1, entry 1)

The reaction of entry 1 in Table 1 is representative. Cesium carbonate (0.23 g, 0.72 mmol) was placed in a 30–mL two–necked reaction flask equipped with a Dimroth condenser. The cesium carbonate was dried in vacuo by heating with a hair dryer for 2 min. Palladium acetate (5.6 mg, 0.025 mmol) was added to the reaction flask. The flask was then filled with argon by using standard Schlenk technique. Tricyclohexylphosphine (0.50 M in toluene, 0.10 mL, 0.050 mmol) and toluene (0.50 mL) were added and the resulting mixture was stirred for 10 min at room temperature. Toluene (1.5 mL), homoallyl alcohol **4** (73 mg, 0.60 mmol), and *o*–chlorotoluene (58 mL, 0.50 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 17 h. After the mixture was cooled to room temperature, water (20 mL) was added. The product was extracted with hexane (20 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification with hexane as an eluent gave 2–(3–methyl–2–butenyl)toluene (**5a**, 0.080 g, 0.50 mmol) in 100% yield.

Characterization Data

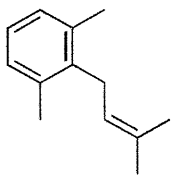
The spectral data of **4**,[5b] , **5e**,[9] **5h**,[10] **5i**,[11] **5j**,[12] and **7b**[13] can be found in the literature.

2–(3–Methyl–2–butenyl)toluene (5a)



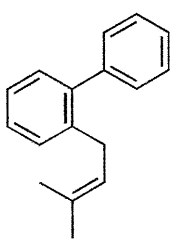
IR (neat) 2971, 1490, 1451, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3H), 1.74 (s, 3H), 2.29 (s, 3H), 3.30 (d, J = 7.0 Hz, 2H,), 5.22–5.26 (m, 1H), 7.08–7.14 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.84, 19.46, 25.73, 32.16, 122.49, 125.87, 125.93, 128.56, 130.01, 132.36, 136.12, 139.92. Found: C, 89.75; H, 9.94%. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06%.

1,3–Dimethyl–2–(3–methyl–2–butenyl)benzene (5b)



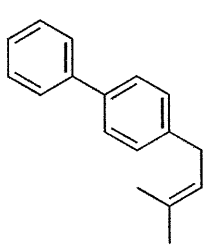
IR (neat) 2977, 1472, 1376, 1099 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 3H), 1.78 (s, 3H), 2.30 (s, 6H), 3.33 (d, J = 6.5 Hz, 2H), 4.97–5.01 (m, 1H), 7.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 17.93, 20.01, 25.63, 28.78, 121.94, 125.65, 128.00, 131.63, 136.25, 138.51. Found: C, 89.43; H, 10.42%. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41%.

2–(3–Methyl–2–butenyl)biphenyl (5c)



IR (neat) 2973, 1479, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 3H), 1.68 (s, 3H), 3.28 (d, J = 7.0 Hz, 2H), 5.17–5.21 (m, 1H), 7.21–7.62 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 17.69, 25.69, 31.98, 123.64, 125.67, 126.70, 127.42, 127.98, 129.25, 129.33, 129.94, 131.94, 139.23, 141.74, 141.81. Found: C, 91.94; H, 8.26%. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16%.

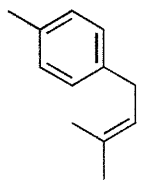
4–(3–Methyl–2–butenyl)biphenyl (5d)



IR (nujol) 2982, 1734, 1558, 1489 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (s, 3H), 1.78 (s, 3H), 3.40 (d, J = 7.5 Hz, 2H), 5.36–5.40 (m, 1H), 7.25–7.28 (m, 2H), 7.32–7.35 (m, 1H), 7.41–7.45 (m, 2H), 7.51–7.54 (m, 2H) 7.57–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.85, 25.78, 33.99, 123.01, 126.96,

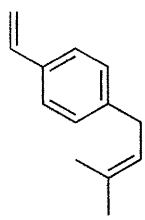
127.01, 127.12, 128.68, 128.70, 132.71, 138.71, 140.94, 141.15. HRMS (EI) Found: 222.1404 [M^+]; Calcd for $C_{17}H_{18}$: 222.1409. Amorphous.

4–(3–Methyl–2–butenyl)toluene (5f)



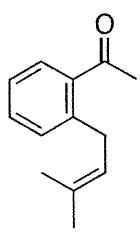
IR (neat) 2975, 1516, 1104 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (s, 3H), 1.78 (s, 3H), 2.36 (s, 3H), 3.35 (d, J = 7.0 Hz, 2H), 5.34–5.38 (m, 1H), 7.12 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 17.77, 20.96, 25.74, 33.91,123.48, 128.16, 129.03, 132.20, 135.10, 138.73. HRMS (EI) Found: 160.1254 [M^+]; Calcd for $C_{12}H_{16}$: 160.1252.

4–(3–Methyl–2–butenyl)styrene (5g)



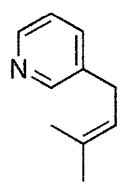
IR (neat) 1684, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (s, 3H), 1.80 (s, 3H), 3.38 (d, J = 7.5 Hz, 2H), 5.23 (d, J = 11.0 Hz, 1H), 5.35–5.39 (m, 1H), 5.75 (d, J = 18.0 Hz, 1H), 6.74 (dd, J = 18.0, 11.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.79, 25.73, 34.07, 112.85, 122.99, 126.21, 128.42, 132.58, 135.16, 136.67, 141.53. Found: C, 90.38; H, 9.58%. Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36%.

Methyl 2–(3–methyl–2–butenyl)phenyl ketone (5k)



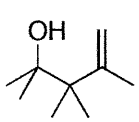
IR (neat) 1684, 1253 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (s, 3H), 1.72 (s, 3H), 2.56 (s, 3H), 3.58 (d, J = 7.0 Hz, 2H), 5.22–5.26 (m, 1H), 7.24–7.29 (m, 2H), 7.37–7.40 (m, 1H), 7.59 (dd, J = 7.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.90, 25.73, 29.96, 32.31, 123.02, 125.68, 128.62, 130.62, 131.27, 132.75, 138.33, 141.35, 202.61. HRMS (EI) Found: 188.1195 [M^+]; Calcd for $C_{13}H_{16}O$: 188.1201.

3–(3–Methyl–2–butenyl)pyridine (5l)



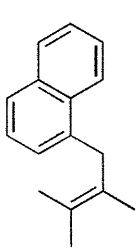
IR (neat) 2977, 1576, 1423, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3H), 1.75 (s, 3H), 3.34 (d, J = 7.5 Hz, 2H), 5.27–5.30 (m, 1H), 7.19–7.21 (m, 1H), 7.47–7.49 (m, 1H), 8.42–8.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.85, 25.69, 31.50, 121.76, 123.29, 129.79, 133.76, 135.77, 147.11, 149.82. HRMS (EI) Found: 147.1046 [M^+]; Calcd for $C_{10}H_{13}N$: 147.1048.

2,3,3,4–Tetramethyl–4–penten–2–ol (6)



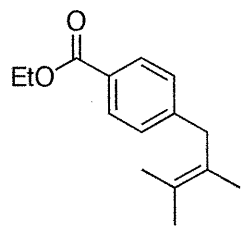
IR (neat) 3447, 2978, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 6H), 1.19 (s, 6H), 1.87 (s, 3H), 4.86 (s, 1H), 5.01 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.57, 23.72, 25.88, 45.67, 74.27, 113.47, 151.58. HRMS (EI) Found: 125.1334 [M–OH]$^+$; Calcd for C_9H_{17}: 125.1330.

1–(2,3–Dimethyl–2–butenyl)naphthalene (7a)



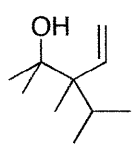
IR (neat) 1505, 1380, 1202 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (s, 3H), 1.81 (s, 3H), 1.84 (s, 3H), 3.78 (s, 2H), 7.26–7.27(m, 1H), 7.41–7.44 (m, 1H), 7.49–7.55 (m, 2H), 7.73–7.75 (m, 1H), 7.88–7.90 (m, 1H), 8.07–8.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.67, 20.57, 20.71, 36.95, 123.56, 125.05, 125.35, 125.46, 125.61, 125.65, 126.39, 126.65, 128.64, 132.58, 133.73, 136.18. Found: C, 91.41; H, 8.75%. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63%.

Ethyl 4–(2,3–dimethyl–2–butenyl)benzoate (7c)



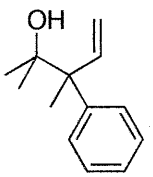
IR (neat) 1718, 1275, 1106 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3H), 1.58 (s, 3H), 1.74 (s, 3H) 1.78 (s, 3H), 3.50 (s, 2H), 4.36 (q, J = 7.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.35, 18.39, 20.61, 20.70, 40.19, 60.71, 125.58, 126.55, 128.03, 128.36, 129.55, 146.62, 166.72; Found: C, 77.41; H, 8.71%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

2,3–Dimethyl–3–(1–methylethyl)–4–penten–2–ol (8a)



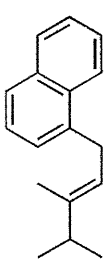
IR (neat) 3566, 2979, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, J = 6.5 Hz, 3H), 0.96 (s, 3H), 0.98 (d, J = 6.5 Hz, 3H), 1.19 (s, 3H), 1.23 (s, 3H), 1.90 (m, 1H), 5.03 (d, J = 17.5 Hz, 1H), 5.26 (d, J = 11.0 Hz, 1H), 5.88 (dd, J = 17.5, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.86, 19.27, 20.23, 26.24, 27.30, 32.37, 49.70, 74.84, 114.51, 144.53. HRMS (EI) Found: 139.1489 $[M–OH]^+$; Calcd for $C_{10}H_{19}$: 139.1487.

2,3–Dimethyl–3–phenyl–4–penten–2–ol (8b)



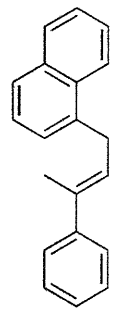
IR (neat) 3566, 2981, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.18 (s, 3H), 1.54 (s, 3H), 5.14 (d, J = 17.5 Hz, 1H), 5.25 (d, J = 11.0 Hz, 1H), 6.74 (dd, J = 17.5, 11.0 Hz, 1H), 7.20–7.24 (m, 1H), 7.29–7.33 (m, 2H), 7.46–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.14, 25.84, 26.05, 51.18, 74.50, 114.43, 126.14, 127.65, 128.47, 143.58, 144.99. HRMS (FAB) Found: 189.1280 [M–H]$^+$; Calcd for $C_{13}H_{17}O$: 189.1279.

(*E*)–1–(3,4–Dimethyl–2–pentenyl)naphthalene (9a)



IR (neat) 2961, 1506 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 6.5 Hz, 6H), 1.77 (s, 3H), 2.29–2.34 (m, 1H), 3.79 (d, J = 7.0 Hz, 2H), 5.04–5.44 (m, 1H), 7.33–7.35 (m, 1H), 7.39–7.42 (m, 1H), 7.47–7.53 (m, 2H), 7.71–7.73 (m, 1H), 7.85–7.87 (m, 1H), 8.02–8.04 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.65, 21.45, 31.46, 36.82, 120.34, 124.05, 125.41, 125.47, 125.61, 125.64, 126.51, 128.62, 132.13, 133.81, 137.86, 142.25. HRMS (EI) Found: 224.1566 [M^+]; Calcd for $C_{17}H_{20}$: 224,1565.

(*E*)–1–(3–Phenyl–2–butenyl)naphthalene (9b)



IR (neat) 3054, 1507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 4.01 (d, J = 7.0 Hz, 2H), 6.04–6.08 (m, 1H), 7.21–7.26 (m, 1H), 7.29–7.34 (m, 2H), 7.40–7.44 (m, 4H), 7.49–7.56 (m, 2H), 7.75–7.77 (m, 1H), 7.88–7.90 (m, 1H), 8.07–8.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.06, 32.51, 123.94, 125.54, 125.63, 125.71, 125.80, 125.89, 126.61, 126.74, 126.84, 128.17, 128.71, 132.06, 133.88, 135.78, 137.03, 143.47. HRMS (EI) Found: 258.1404 [M^+]; Calcd for $C_{20}H_{18}$: 258.1409.

References and Notes

1. For reviews: (a) Knölker, H.–J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427. (b) Tahara, S.; Ibrahim, R. K. *Phytochemistry* **1995**, *38*, 1073–1094.
2. (a) Knölker, H.–J.; Fröhner, W. *Synlett* **1997**, 1108–1110. (b) Fröhner, W.; Reddy, K. R.; Knölker, H.–J. *Heterocycles* **2007**, *74*, 895–912. c) Knölker, H.–J. *Chem. Lett.* **2009**, *38*, 8–13.
3. Selected examples: (a) Mizuno, K.; Ikeda, M.; Otsuji, Y. *Tetrahedron Lett.* **1985**, *26*, 461–464. (b) Nakanishi, K.; Mizuno, K.; Otsuji, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2371–2379. (c) Jung, Y.–S.; Joe, B.–Y.; Seong, C.–M.; Park, N.–S. *Bull. Korean Chem. Soc.* **2000**, *21*, 463–464.
4. Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6511–6514.
5. (a) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211. (b) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4463–4469. (c) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2007**, *63*, 5200–5203. (d) Hayashi, S.; Hirano, K.; Yorimitsu, H. ; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 12650–12651. (e) Yorimitsu, H.; Oshima, K. *J. Synth. Org. Chem., Jpn.* **2008**, *66*, 332–343.
6. In the reactions in Table 1, the use of aryl bromides or iodides generally resulted in lower yields. Excessively smooth oxidative addition would disorder the catalytic cycle.
7. Reviews for microwave–assisted organic reactions: (a) *Microwave Assisted Organic Synthesis*, Tierney, J. P.; Lidström, P. Eds., Blackwell Publishing: Victoria, 2005. (b) Tokuyama, H.; Nakamura, M. *J. Synth. Org. Chem., Jpn.* **2005**, *63*, 523–538. (c) de la Hoz, A.; Diaz–Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178. (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284. (e) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283. (f) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1–47.

8. Heitz, W.; Brugging, W.; Freund, L.; Gailberger, M.; Greiner, A.; Jung, H.; Kampschulte, U.; Niessner, N.; Osan, F.; Schmidt, H. W.; Wicker, M. *Makromol. Chem.* **1988**, *189*, 119–127.
9. Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265–8268.
10. Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kočovský, P. *J. Org. Chem.* **1999**, *64*, 2751–2764.
11. Knapp, S.; Albaneze, J.; Schugar, H. J. *J. Org. Chem.* **1993**, *58*, 997–998.
12. Lee, P. H.; Sung, S.–Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201–3204.
13. Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2002**, 2210–2211.

Chapter 4

Synthesis of (2–Arylethylidene)cyclobutanes by Palladium–Catalyzed Reactions of Aryl Halides with Homoallyl Alcohols Bearing a Trimethylene Group at the Allylic Position

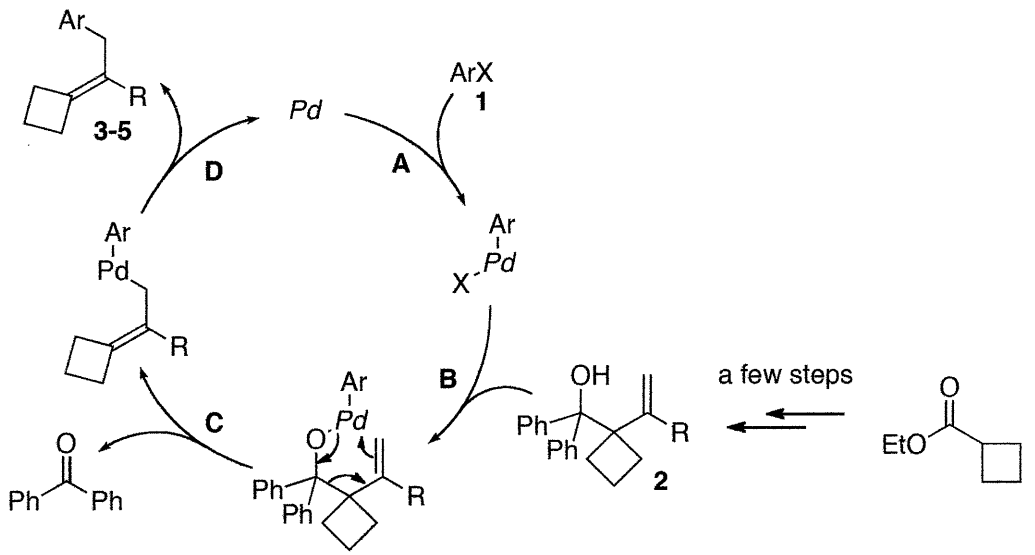
Treatment of aryl bromides with homoallyl alcohols bearing a trimethylene group at the allylic position in the presence of cesium carbonate under palladium catalysis affords (2–arylethylidene)cyclobutanes selectively. The selective formation of the alkylidenecyclobutane skeleton results from regiospecific retro–allylation of the homoallyl alcohols, which accompanies the transposition of the double bonds.

Introduction

Alkylidenecyclobutanes are interesting compounds due to their strained skeleton and reactive double bonds and are hence useful in organic synthesis.[1] Uncatalyzed[2] and catalyzed[3] cycloaddition reactions of allenes with activated alkenes represent conventionally the most useful method for the synthesis of alkylidenecyclobutanes. However, the use of activated alkenes such as acrylonitrile and styrene limits the scope of the reactions. The Wittig alkylidenation reactions of cyclobutanone seem to be secure, unfortunately suffering from moderate yields.[4] Titanium reagents engage in preparation of alkylidenecyclobutanes although the strong oxophilicity of the reagents leads to limited functional group compatibility.[1b,5] A new efficient method for constructing this intriguing strained skeleton has been awaited.

Palladium–catalyzed reactions of aryl halides with homoallyl alcohols that result in highly regiospecific synthesis of allylarenes were reported.[6,7] The author envisioned that the allylation reaction of aryl halides would be applicable to the synthesis of alkylidenecyclobutanes by using homoallyl alcohol **2** bearing a trimethylene group at the allylic position (Scheme 1 and Table 1). After oxidative addition (Step **A**), alkoxide–halide exchange between arylpalladium halide and **2** would occur to yield aryl(alkoxy)palladium (Step **B**). The subsequent retro–allylation of the palladium alkoxide would afford aryl(3–trimethylene–2–propenyl)palladium regioselectively with releasing benzophenone (Step **C**). Finally, immediate reductive elimination would lead to the regioselective synthesis of alkylidenecyclobutanes without forming the regioisomer, (3–trimethylene–2–propenyl)arene (Step **D**). Advantageously, alcohols **2** were readily prepared in a few steps from commercially available ethyl cyclobutanecarboxylate.[8]

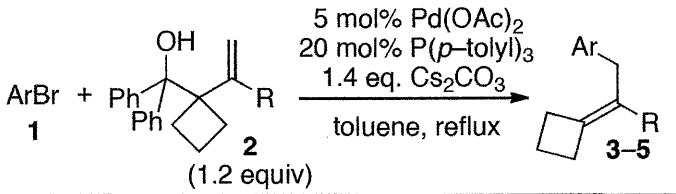
Scheme 1. Proposal for the construction of alkylidenecyclobutanes



Results and Discussion

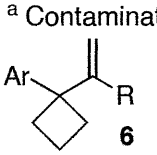
Treatment of 2–bromonaphthalene (**1a**) with alcohol **2a** in the presence of cesium carbonate and catalytic amounts of palladium acetate and tri–4–tolylphosphine in toluene at reflux provided alkylidenecyclobutane **3a** in 94% yield (Table 1, entry 1). Sterically demanding **1b** and **1c** also participated in the reaction (entries 2 and 3). Electron–deficient aryl bromides reacted smoothly to afford the corresponding products in excellent yields (entries 6 and 7). The reaction of aryl bromide **1h** bearing an electron donating *p*–methoxy group provided **3h** in 66% yield (entry 8). A carbon–carbon bond formation took place predominantly at the brominated carbon of **1i**, leaving the chloro moiety intact (entry 9). The reaction of ethyl 2–bromobenzoate (**1j**) gave rise to a modest yield (entry 10). The reactions of 3,5–dimethylbromobenzene (**1d**) and 2–bromoanisole (**1k**) yielded the corresponding alkylidenecyclobutanes **3d** and **3k**, respectively, although the products were contaminated with 5% yields of regioisomers **6** (entries 4 and 11). Vinyl bromide **1l** also underwent the reaction to yield the corresponding 1,4–diene (entry 12). The methyl group of **2a** was not essential. Phenyl–substituted **2b** as well as **2c** bearing no substituents on the vinyl group also underwent the reaction (entries 13–17).

Table 1. Synthesis of (2–Arylethylidene)cyclobutanes



entry	Ar	1	R	2	time (h)	3–5	yield (%)
1	2–naphthyl	**1a**	Me	**2a**	13	**3a**	94
2	1–naphthyl	**1b**	Me	**2a**	13	**3b**	94
3	2–PhC_6H_4	**1c**	Me	**2a**	9	**3c**	67
4	3,5–$Me_2C_6H_3$	**1d**	Me	**2a**	9	**3d**	61[a]
5	4–PhC_6H_4	**1e**	Me	**2a**	9	**3e**	70
6	4–$CF_3C_6H_4$	**1f**	Me	**2a**	10	**3f**	87
7	4–$EtO_2CC_6H_4$	**1g**	Me	**2a**	13	**3g**	97
8	4–$MeOC_6H_4$	**1h**	Me	**2a**	13	**3h**	66
9	4–ClC_6H_4	**1i**	Me	**2a**	10	**3i**	66
10	2–$EtO_2CC_6H_4$	**1j**	Me	**2a**	12	**3j**	53
11	2–$MeOC_6H_4$	**1k**	Me	**2a**	12	**3k**	71[a]
12	(CH_2=CBrPh)	**1l**	Me	**2a**	10	**3l**	60
13	2–naphthyl	**1a**	Ph	**2b**	11	**4a**	75
14	4–$EtO_2CC_6H_4$	**1g**	Ph	**2b**	16	**4g**	82
15	4–$MeOC_6H_4$	**1h**	Ph	**2b**	16	**4h**	78
16	2–naphthyl	**1a**	H	**2c**	18	**5a**	62
17	4–$EtO_2CC_6H_4$	**1g**	H	**2c**	18	**5g**	87

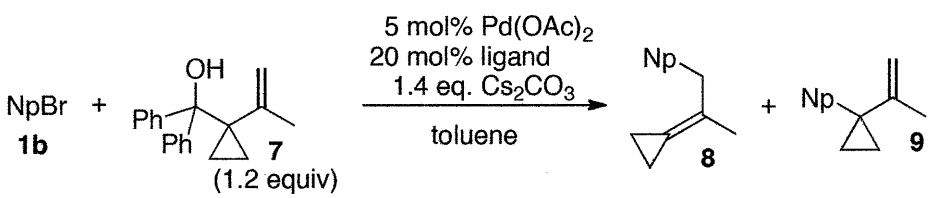
[a] Contaminated with regioisomer **6** (5%).



The author attempted the synthesis of alkylidenecyclopropane by applying the present strategy (Table 2). However, the reaction with **7** under the standard reaction conditions was sluggish (entry 1). The rigid cyclopropane moieties of alcohols **7** would hamper the retro–allylation step probably due to the wider and fixed C(hydroxylated)–C(cyclopropyl)–C(vinylic) angle (calculated to be 114°)[9] than the calculated

C(hydroxylated)–C(cyclobutyl)–C(vinylic) angle of **2a** (110°)[9] as well as the typical unstrained C–C(sp^3)–C angle (*ca.* 110°). The high strain energy of methylenecyclopropane skeleton is also responsible for the difficulty. According to the literature,[10] the strain energy of methylenecyclobutane (26.9 kcal/mol) is close to that of cyclobutane (26.5 kcal/mol). In contrast, the strain energy of methylenecyclopropane (40.9 kcal/mol) was calculated to be much larger than that of cyclopropane (27.5 kcal/mol). The retro–allylation of **7** would thus require the higher activation energy than that of **2**. With heating the reaction mixture at 250 °C under microwave irradiation, the reaction afforded desired **8** exclusively, albeit in modest yield (entry 2).

Table 2. Synthesis of (2–Arylethylidene)cyclopropanes



entry	heating	time	ligand	**8** (%)	**9** (%)
1	conventional (110 °C)	11 h	P(*p*–tol)$_3$	< 26	0
2	microwave (250 °C)	15 min	P(*p*–tol)$_3$	41	0
3	microwave (250 °C)	15 min	PMe_3	0	59

Interestingly, the use of trimethylphosphine instead of tri–*p*–tolylphosphine reversed the regioselectivity and **9** was solely obtained (entry 3). The author assumes that the small and electron–donating trimethylphosphine retarded smooth reductive elimination from intermediate **10** (Scheme 2). The slow reductive elimination would lead to the isomerization of **10** to thermodynamically more stable **11**, from which reductive elimination would occur. Unfortunately, such a drastic change in regioselectivity was not observed in the reactions of **2**.

Scheme 2. Isomerization of (3–Ethylene–2–methyl–2–propenyl)palladium

Conclusion

The author has developed a new access to (2–arylethylidene)cyclobutanes, using the palladium–catalyzed retro–allylation of homoallyl alcohols **2** as a method for the transposition of the double bond.

Experimental Section

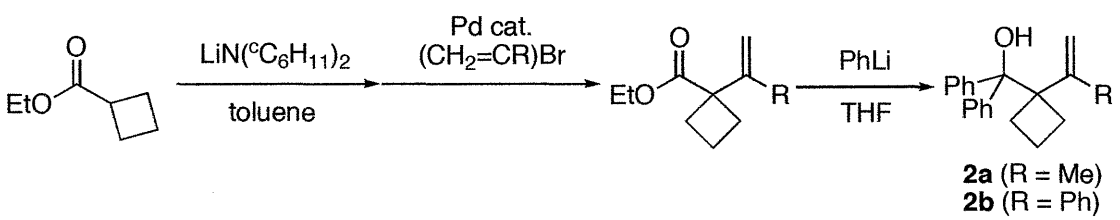
Instrumentation

^{1}H NMR (300 MHz and 500 MHz) and ^{13}C NMR (75.3 MHz and 125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to residual $CHCl_3$ at 77.0 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra (EI unless otherwise noted) were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Chemicals

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene was purchased from Wako Pure Chemical Co. and stored over slices of sodium. Tri-4-tolylphosphine and cesium carbonate were purchased from Wako Pure Chemical Co. Palladium acetate was obtained from TCI. Trimethylphosphine was obtained from Aldrich. The preparations of the homoallyl alcohols **2** are described in the following section. All reactions were carried out under argon atmosphere.

Preparation of homoallyl alcohol 2a and 2b



2a (R = Me)
2b (R = Ph)

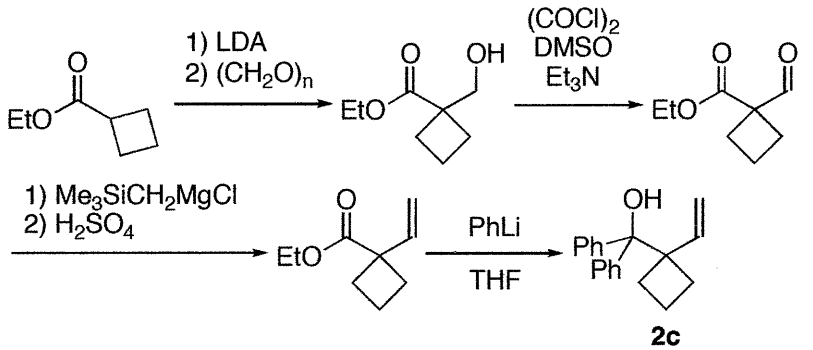
Preparation of homoallyl alcohol **2a** is representative. Under argon atmosphere,

butyllithium (1.6 M hexane solution, 16 mL, 26 mmol) was placed in a 100–mL reaction flask. Dicyclohexylamine (6.0 mL, 30 mmol) in toluene (40 mL) was added dropwise at 0 °C. After 1 h, ethyl cyclobutanecarboxylate (3.0 mL, 22 mmol) was slowly added to this solution. The resultant solution was stirred at room temperature for 1 h. Under argon atmosphere, the solution was added to a mixture of 2–bromopropene (1.8 mL, 20 mmol), dipalladium tris(dibenzylideneacetone) (460 mg, 0.50 mmol), and tri–*tert*–butylphosphine (1.0 M in toluene, 1.0 mL, 1.0 mmol) in another 100–mL reaction flask. The flask that had contained the enolate was washed with 5 mL of toluene. This washing solution was added to the reaction mixture. The reaction mixture was then stirred at room temperature for 10 h. The reaction mixture was diluted with ethyl acetate (30 mL). The resulting solution was washed with 1 M hydrochloric acid (10 mL), and the aqueous layer was washed with ethyl acetate (10 mL × 3). The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. The residue was then purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to afford the corresponding ester in 62% yield (2.1 g, 12 mmol).

Under argon atmosphere, phenyllithium (1.09 M cyclohexane/ethereal solution, 27 mL, 30 mmol) was placed in a 100–mL reaction flask. The ester (2.1 g, 12 mmol) in THF (15 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was poured into saturated ammonium chloride solution (30 mL). The product was extracted with ethyl acetate (30 mL × 3), and organic layers were washed with brine. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. The product was chromatographed on silica gel (hexane/ether = 20:1) to afford **2a** (1.51 g, 5.43 mmol, 45%).

Homoallyl alcohol **2b** was prepared in a fashion similar to that of **2a**. The Alkenylation of ethyl cyclobutanecarboxylate (1.5 mL, 11 mmol) with α–bromostyrene (1.3 mL, 10 mmol) provided 1.3 g of ethyl (1–phenylethenyl)cyclobutanecarboxylate (5.6 mmol, 56% yield). The phenylation of the ester (1.3 g, 5.6 mmol) proceeded quantitatively and provided 1.53 g of **2b** (5.38 mmol, 96%).

Preparation of homoallyl alcohol 2c



2c

Under argon atmosphere, butyllithium (1.6 M hexane solution, 8.1 mL, 13 mmol) was placed in a 50–mL reaction flask. Diisopropylamine (2.1 mL, 15 mmol) in THF (10 mL) was added dropwise at 0 °C. After 1 h, ethyl cyclobutanecarboxylate (1.5 mL, 11 mmol) was slowly added to this solution. The resultant solution was stirred at 0 °C for 1 h. Paraformaldehyde (300 mg, 10 mmol) in THF (10 mL) was added dropwise at 0 °C. After being stirred for 2 h at ambient temperature, the mixture was poured into saturated ammonium chloride solution (30 mL). The product was extracted with ethyl acetate (20 mL × 3), and organic layers were washed with brine. The combined organic layers were dried over sodium sulfate, and evaporated in vacuo to yield ethyl 1–(hydroxymethyl)cyclobutanecarboxylate.

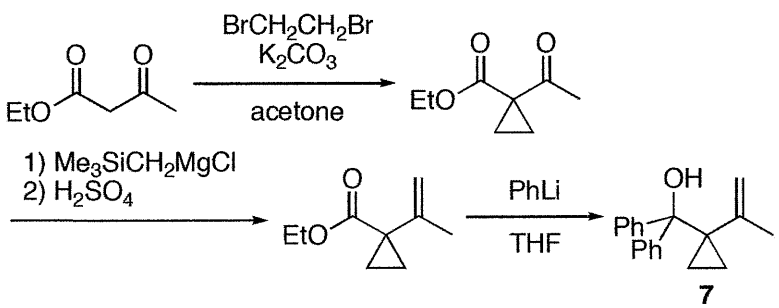
Oxalyl chloride (1.0 mL, 10 mmol) in dichloromethane (10 mL) was placed in a 50–mL reaction flask under argon. Dimethyl sulfoxide (1.4 mL, 20 mmol) was added to the stirred solution at –78 °C. After 10 min, a solution of the crude alcohol in dichloromethane (10 mL) was added to the reaction mixture. After 30 min, the reaction mixture was treated with triethylamine (5.6 mL, 40 mmol) and then allowed to warm to 0 °C. After 3 h, the reaction mixture was poured into brine and extracted with dichloromethane (20 mL × 3). The combined organic layers were dried over sodium sulfate, and evaporated in vacuo to yield ethyl 1–formylcyclobutanecarboxylate.

Trimethylsilylmethylmagnesium bromide (1.0 M THF solution, 12 mL, 12 mmol) was placed in a 50–mL reaction flask under an atmosphere of argon. The crude aldehyde in THF (10

mL) was added to the Grignard reagent dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was poured into saturated ammonium chloride solution (30 mL). The product was extracted with ethyl acetate (30 mL × 3), and organic layers were washed with brine. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. Under argon atmosphere, the crude ester in THF (10 mL) was placed in a 100–mL reaction flask. Concentrated sulfuric acid (1.0 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was poured into 4 M sodium hydroxide solution (10 mL). The product was extracted with ethyl acetate (10 mL × 3), and organic layers were washed with brine. The combined organic layer was dried over sodium sulfate, and concentrated in vacuo to afford ethyl 1–vinylcyclobutanecarboxylate as a crude oil.

Under argon atmosphere, phenyllithium (1.09 M cyclohexane/ethereal solution, 22 mL, 24 mmol) was placed in a 100–mL reaction flask. The crude ester in THF (10 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was poured into saturated ammonium chloride solution (30 mL). The product was extracted with ethyl acetate (30 mL × 3), and organic layers were washed with brine. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. The product was chromatographed on silica gel (hexane/ether = 10:1) to afford **2c** (783 mg, 2.96 mmol, 30% overall).

Preparation of homoallyl alcohol 7



7

Powdered anhydrous potassium carbonate (28 g, 200 mmol) was placed in a 300–mL

reaction flask. Ethyl acetoacetate (6.4 mL, 50 mmol) in acetone (200 mL) was added. The mixture was vigorously stirred. 1,2–Dibromoethane (5.2 mL, 60 mmol) was added and stirred at room temperature for 24 h. The reaction mixture was poured into brine and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over sodium sulfate, and evaporated in vacuo. The product was chromatographed on silica gel (hexane/ether = 5:1) to afford ethyl 1–acetylcyclopropanecarboxylate (5.37 g, 34.4 mmol, 69%).

Under argon atmosphere, trimethylsilylmethylmagnesium bromide (1.0 M THF solution, 41 mL, 41 mmol) was placed in a 100–mL reaction flask. The ester (5.4 g, 34 mmol) in THF (10 mL) was added to the Grignard reagent dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was poured into saturated ammonium chloride solution (50 mL). The product was extracted with ethyl acetate (30 mL × 3), and organic layers were washed with brine. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. Under argon atmosphere, the crude ester in THF (30 mL) was placed in a 200–mL reaction flask. Concentrated sulfuric acid (5.0 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was poured into 4 M sodium hydroxide solution (30 mL). The product was extracted with ethyl acetate (30 mL × 3), and organic layers were washed with brine. The combined organic layer was dried over sodium sulfate, and concentrated in vacuo to afford ethyl 1–isopropenylcyclopropanecarboxylate (3.16 g, 20.5 mmol, 60%) as a crude oil.

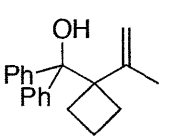
Under argon atmosphere, phenyllithium (0.98 M cyclohexane/ethereal solution, 50 mL, 49 mmol) was placed in a 100–mL reaction flask. The crude ester (3.2 g, 21 mmol) in THF (10 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was poured into saturated ammonium chloride solution (50 mL). The product was extracted with ethyl acetate (30 mL × 3), and organic layers were washed with brine. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. The product was chromatographed on silica gel (hexane/ether = 20:1) to afford **7** (3.88 g, 14.6 mmol, 70%).

Typical Procedure

Cesium carbonate (0.12 g, 0.36 mmol) was placed in a 20–mL two–necked reaction flask equipped with a Dimroth condenser. The cesium carbonate was dried in vacuo with heating with a hair dryer for 2 min. Palladium acetate (2.8 mg, 0.0125 mmol) and tri–4–tolylphosphine (15 mg, 0.050 mmol) were added to the reaction flask. The flask was then filled with argon by using the standard Schlenk technique. Toluene (2.0 mL), homoallyl alcohol **2a** (79 mg, 0.30 mmol), and 2–bromonaphthalene (**1a**, 52 mg, 0.25 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 13 h. After the mixture was cooled to room temperature, water (20 mL) was added. The product was extracted with hexane (20 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification with hexane as an eluent gave 2–(2–cyclobutylidenepropyl)naphthalene (**3a**, 52.0 mg, 0.234 mmol) in 94% yield.

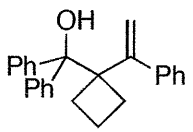
Characterization of Compounds

(1–Isopropenylcyclobutyl)diphenymethanol (2a)



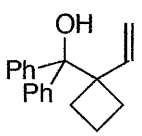
IR (neat) 3545, 3022, 2921, 1448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11–1.19 (m, 1H), 1.54 (s, 3H), 1.59–1.65 (m, 1H), 2.17–2.24 (m, 2H), 2.50–2.56 (m, 2H), 2.84 (s, 1H), 5.13 (s, 2H), 7.21–7.24 (m, 2H), 7.28–7.31 (m, 4H), 7.60–7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.13, 22.43, 30.35, 56.88, 79.26, 116.23, 126.67, 127.35, 127.82, 145.04, 149.99. Found: C, 86.50; H, 8.23%. Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97%.

Diphenyl[1–(1–phenylethenyl)cyclobutyl]methanol (2b)



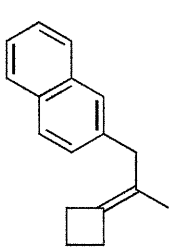
IR (nujol) 3546, 1447 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93–1.02 (m, 1H), 1.69–1.78 (m, 1H), 2.06 (s, 1H), 2.60–2.64 (m, 4H), 5.08 (s, 1H), 5.58 (s, 1H), 6.68–6.70 (m, 2H), 7.11–7.14 (m, 2H), 7.18–7.25 (m, 7H), 7.40–7.42 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 15.62, 30.08, 56.69, 80.92, 118.45, 126.57, 127.15, 127.91, 128.06, 128.73, 128.92, 143.69, 145.35, 153.74. Found: C, 88.33; H, 7.22%. Calcd for $C_{25}H_{24}O$: C, 88.20; H, 7.11%. m.p. 99.1–99.9 °C.

(1–Ethenylcyclobutyl)diphenylmethanol (2c)



IR (neat) 3553, 2867, 1447 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38–1.46 (m, 1H), 1.73–1.82 (m, 1H), 1.97–2.02 (m, 2H), 2.41 (s, 1H), 2.53–2.59 (m, 2H), 5.21 (dd, J = 11.0, 1.5 Hz, 1H), 5.34 (dd, J = 17.5, 1.5 Hz, 1H), 6.11 (dd, J = 17.5, 11.0 Hz, 1H), 7.21–7.24 (m, 2H), 7.27–7.30 (m, 4H), 7.39–7.41 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 15.29, 28.19, 52.74, 80.47, 114.43, 126.78, 127.49, 128.08, 143.10, 144.92. Found: C, 86.43; H, 7.92%. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63%.

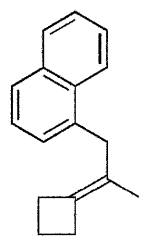
2–(2–Cyclobutylidenepropyl)naphthalene (3a)



IR (neat) 2826, 1600, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H), 1.95–2.01 (m, 2H), 2.68–2.72 (m, 2H), 2.80–2.82 (m, 2H), 3.35 (s, 2H), 7.30–7.32 (m, 1H), 7.40–7.47 (m, 2H), 7.60 (s, 1H), 7.75–7.81 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 15.68, 15.86, 29.26, 29.43, 38.95, 124.83,

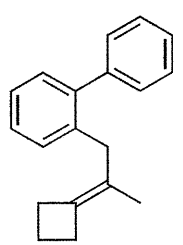
125.02, 125.78, 126.69, 127.42, 127.53, 127.58, 127.76, 132.02, 133.59, 134.38, 138.40. Found: C, 91.57; H, 8.06%. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16%.

1–(2–Cyclobutylidenepropyl)naphthalene (3b)



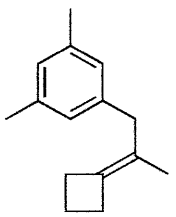
IR (neat) 2909, 1596, 1509 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.94–2.00 (m, 2H), 2.69–2.76 (m, 4H), 3.67 (s, 2H), 7.32–7.33 (m, 1H), 7.39–7.43 (m, 1H), 7.46–7.53 (m, 2H), 7.72–7.73 (m, 1H), 7.85–7.87 (m, 1H), 8.05–8.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.95, 16.02, 29.40, 29.42, 35.83, 123.90, 124.30, 125.36, 125.48, 125.59, 126.31, 126.55, 128.58, 132.48, 133.73, 134.51, 136.43. Found: C, 91.78; H, 8.17%. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16%.

2–(2–Cyclobutylidenepropyl)biphenyl (3c)



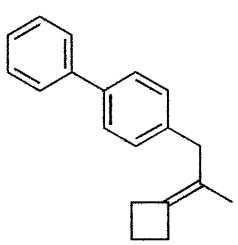
IR (neat) 3028, 1477 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.80 –1.86 (m, 2H), 2.39–2.42 (m, 2H), 2.56–2.61 (m, 2H), 3.17 (s, 2H), 7.19–7.47 (m, 8H), 7.59–7.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.66, 15.80, 29.06, 29.17, 35.82, 124.53, 125.62, 126.64, 127.15, 127.21, 127.90, 128.73, 129.31, 129.34, 129.90, 134.43, 137.77. Found: C, 91.64; H, 8.00%. Calcd for $C_{19}H_{20}$: C, 91.88; H, 8.12%.

1–(2–Cyclobutylidenepropyl)–3,5–dimethylbenzene (3d)



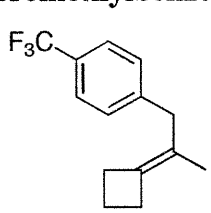
IR (neat) 2917, 1602, 1443 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.91–1.98 (m, 2H), 2.29 (s, 6H), 2.65–2.69 (m, 2H), 2.74–2.77 (m, 2H), 3.11 (s, 2H), 6.78 (s, 2H), 6.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.65, 15.81, 21.31, 29.20, 29.34, 38.55, 125.04, 126.48, 127.37, 133.85, 137.65, 140.70. Found: C, 90.10; H, 10.33%. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06%.

4–(2–Cyclobutylidenepropyl)biphenyl (3e)



IR (neat) 2908, 1486 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3H), 1.93–1.99 (m, 2H), 2.66–2.70 (m, 2H), 2.76–2.79 (m, 2H), 3.23(s, 2H), 7.23–7.25 (m, 2H), 7.31–7.34 (m, 1H), 7.41–7.45 (m, 2H), 7.50–7.52 (m, 2H), 7.57–7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.70, 15.83, 29.22, 29.36, 38.38, 124.81, 126.94, 126.98, 126.99, 128.68, 129.06, 134.31, 138.68, 139.97, 141.15. Found: C, 91.64; H, 8.00%. Calcd for $C_{19}H_{20}$: C, 91.88; H, 8.12%.

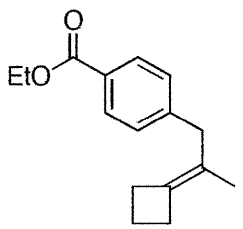
1–(2–Cyclobutylidenepropyl)–4–trifluoromethylbenzene (3f)



IR (neat) 2915, 1618, 1326 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.94–2.00 (m, 2H), 2.66–2.71 (m, 2H), 2.73–2.76 (m, 2H), 3.25 (s, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz,

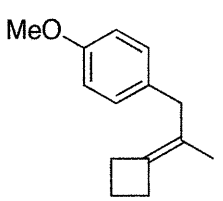
2H); ^{13}C NMR ($CDCl_3$) δ 15.61, 15.78, 29.20, 29.32, 38.60, 123.99, 124.41 (q, J = 270 Hz), 125.15 (q, J = 3.9 Hz), 128.13 (q, J = 32 Hz), 128.90, 135.17, 145.03. Found: C, 70.24; H, 6.54%. Calcd for $C_{14}H_{15}F_3$: C, 69.99; H, 6.29%.

Ethyl 4–(2–cyclobutylidenepropyl)benzoate (3g)



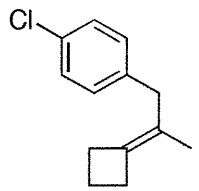
IR (neat) 2910, 1717, 1610, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3H), 1.40 (s, 3H), 1.92–1.98 (m, 2H), 2.65–2.69 (m, 2H), 2.72–2.75 (m, 2H), 3.23 (s, 2H), 4.36 (q, J = 7.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.32, 15.62, 15.77, 29.18, 29.32, 38.81, 60.71, 124.11, 128.10, 128.61, 129.55, 134.93, 146.33, 166.69. Found: C, 78.59; H, 8.49%. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25%.

4–(2–Cyclobutylidenepropyl)anisole (3h)



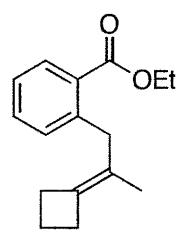
IR (neat) 2910, 1510, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.91–1.98 (m, 2H), 2.65–2.69 (m, 2H), 2.73–2.76 (m, 2H), 3.13 (s, 2H), 3.79 (s, 3H), 6.83 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.54, 15.84, 29.20, 29.32, 37.80, 55.22, 113.63, 125.27, 129.51, 132.86, 133.74, 157.72. Found: C, 83.09; H, 9.27%. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97%.

1–Chloro–4–(2–cyclobutylidenepropyl)benzene (3i)



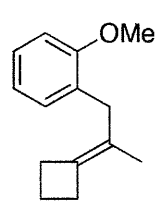
IR (neat) 2910, 1490, 1082 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.92–1.98 (m, 2H), 2.65–2.68 (m, 2H), 2.71–2.74 (m, 2H), 3.15 (s, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.54, 15.80, 29.19, 29.30, 38.08, 124.44, 128.29, 129.97, 131.40, 134.62, 139.25. Found: C, 75.80; H, 7.58%. Calcd for $C_{13}H_{15}Cl$: C, 75.54; H, 7.31%.

Ethyl 2–(2–cyclobutylidenepropyl)benzoate (3j)



IR (neat) 2911, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H), 1.88–1.95 (m, 2H), 2.62–2.69 (m, 4H), 3.59 (s, 2H), 4.36 (q, J = 7.0 Hz, 2H), 7.21–7.26 (m, 2H), 7.39–7.42 (m, 1H), 7.77–7.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.31, 15.83, 15.88, 29.31, 29.33, 35.83, 60.81, 124.45, 125.61, 129.90, 130.07, 131.06, 131.42, 134.98, 141.53, 168.22. Found: C, 78.74; H, 8.47%. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25%.

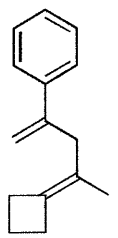
2–(2–Cyclobutylidenepropyl)anisole (3k)



IR (neat) 2911, 1491, 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3H), 1.91–1.97 (m, 2H), 2.67–2.73 (m, 4H), 3.23 (s, 2H), 3.84 (s, 3H), 6.85–6.87 (m, 1H), 6.89–6.92 (m, 1H), 7.12–7.14 (m, 1H), 7.17–7.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.87 (two signals merge.), 29.31 (two signals merge.), 32.05, 55.27, 110.17, 120.28, 124.20, 126.80, 126.85, 129.68, 134.40, 157.61.

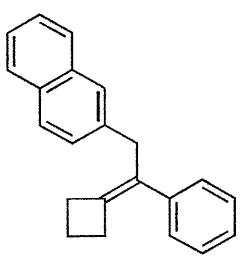
HRMS (EI) Found: 202.1354 [M^+]; Calcd for $C_{14}H_{18}O$:202.1358.

4–Cyclobutylidene–2–phenyl–1–pentene (3l)



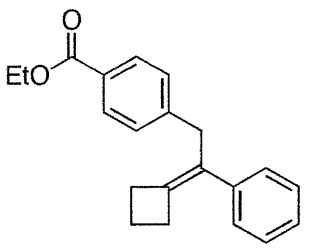
IR (neat) 2911, 1444, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 3H), 1.87–1.93 (m, 2H), 2.61–2.67 (m, 4H), 3.07 (s, 2H), 5.08 (s, 1H), 5.35 (s, 1H), 7.23–7.28 (m, 1H), 7.31–7.34 (m, 2H), 7.43–7.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.64, 15.82, 29.27 (two signals merge.), 38.45, 113.21, 123.31, 126.06, 127.20, 128.05, 134.89, 141.65, 146.08. HRMS (EI) Found: 198.1412 [M^+]; Calcd for $C_{15}H_{18}$: 198.1409.

2–(2–Cyclobutylidene–2–phenylethyl)naphthalene (4a)



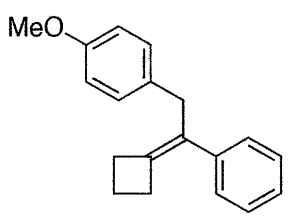
IR (neat) 2924, 2360. 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06–2.12 (m, 2H), 2.93–2.97 (m, 2H), 3.00–3.04 (m, 2H), 3.88 (s, 2H), 7.12–7.15 (m, 1H), 7.23–7.29 (m, 4H), 7.35–7.44 (m, 3H), 7.63 (s, 1H), 7.73–7.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 17.00, 31.19, 32.30, 37.01, 125.00, 125.71, 125.90, 126.28, 127.16, 127.19, 127.49, 127.52, 127.77, 127.97, 128.72, 131.98, 133.60, 138.03, 139.88, 140.91. Found: C, 92.77; H, 7.05%. Calcd for $C_{22}H_{20}$: C, 92.91; H, 7.09%.

Ethyl 4–(2–cyclobutylidene–2–phenylethyl)benzoate (4g)



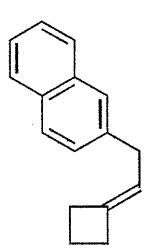
IR (neat) 1715, 1103 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, J = 7.0 Hz, 3H), 2.01–2.08 (m, 2H), 2.86–2.89 (m, 2H), 2.93–2.96 (m, 2H), 3.73 (s, 2H), 4.33 (q, J = 7.0 Hz, 2H), 7.10–7.14 (m, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.21–7.24 (m, 4H), 7.89 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.33, 16.92, 31.09, 32.19, 36.90, 60.71, 126.04, 127.13, 128.03, 128.25, 129.59, 130.06, 132.41, 139.49, 141.18, 146.00, 166.67. Found: C, 82.05; H, 7.16%. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24%.

4–(2–Cyclobutylidene–2–phenylethyl)anisole (4h)



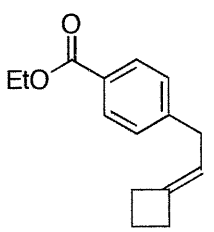
IR (neat) 1511, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00–2.07 (m, 2H), 2.87–2.90 (m, 2H), 2.93–2.96 (m, 2H), 3.63 (s, 2H), 3.75 (s, 3H), 6.77 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 9.0 Hz, 2H), 7.11–7.14 (m, 1H), 7.20–7.25 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.97, 31.09, 32.22, 35.83, 55.16, 113.65, 125.83, 127.20, 127.93, 129.10, 129.18, 132.46, 139.93, 140.29, 157.62. Found: C, 86.04; H, 7.74%. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63%.

2–(2–Cyclobutylidenethyl)naphthalene (5a)



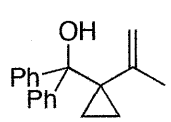
IR (neat) 2913, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98–2.04 (m, 2H), 2.71–2.80 (m, 4H), 3.39 (d, J = 7.5 Hz, 2H), 5.32–5.37 (m, 1H), 7.33–7.35 (m, 1H), 7.40–7.47 (m, 2H), 7.62 (s, 1H), 7.77–7.81 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 16.99, 29.35, 30.92, 34.45, 118.76, 125.05, 125.83, 126.08, 127.36, 127.41, 127.58, 127.85, 131.96, 133.65, 139.12, 141.45. Found: C, 92.04; H, 7.85%. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74%.

Ethyl 4–(2–cyclobutylidenethyl)benzoate (5g)



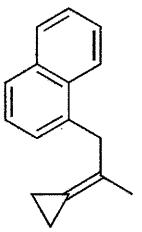
IR (neat) 2924, 2333, 1719, 1274 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3H), 1.95–2.01 (m, 2H), 2.68–2.73 (m, 4H), 3.26 (d, J = 7.5 Hz, 2H), 4.37 (q, J = 7.0 Hz, 2H), 5.21–5.25 (m, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.33, 16.91, 29.27, 30.87, 34.31, 60.74, 117.93, 128,05, 128.26, 129.65, 142.05, 147.02, 166.68. Found: C, 78.52; H, 7.96%. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88%.

(1–Isopropenylcyclopropyl)diphenylmethanol (7)



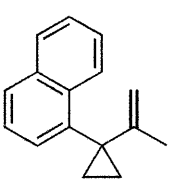
IR (neat) 3527, 2950, 1680, 1447 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66–0.72 (m, 4H), 1.55 (s, 3H), 3.03 (s, 1H), 5.03 (s, 1H), 5.11 (s, 1H), 7.19–7.23 (m, 2H), 7.26–7.30 (m, 4H), 7.59–7.61 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 9.78, 23.84, 34.65, 79.29, 118.95, 126.84, 127.30, 127.89, 144.60, 147.32. Found: C, 86.59; H, 7.70%. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63%.

1–(2–Cyclopropylidenepropyl)naphthalene (8)



IR (neat) 2971, 1596, 1509 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87–0.90 (m, 2H), 0.97–1.00 (m, 2H), 1.80 (s, 3H), 3.93 (s, 2H), 7.33–7.34 (m, 1H), 7.39–7.42 (m, 1H), 7.43–7.47 (m, 2H), 7.72–7.74 (m, 1H), 7.83–7.85 (m, 1H), 8.04–8.06 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 1.80, 3.12, 20.75, 40.45, 117.58, 123.07, 124.32, 125.30, 125.38, 125.49, 126.67, 126.91, 128.52, 132.54, 133.73, 136.43. HRMS (EI) Found: 208.1252 [M^+]; Calcd for $C_{16}H_{16}$: 208.1252.

1–(Isopropenylcyclopropyl)naphthalene (9)



IR (neat) 2857, 1630, 1507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (brs, 2H), 1.29 (brs, 2H), 1.68 (s, 3H), 4.68 (s, 1H), 4.81 (s, 1H), 7.41–7.53 (m, 4H), 7.76 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.62, 20.69, 29.90, 110.55, 125.24, 125.38, 125.45, 125.58, 127.27, 127.91, 128.45, 133.02, 133.84, 140.39, 148.07. Found: C, 92.16; H, 7.63%. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74%.

Computational Details

The structures were optimized by using Spartan '04 program[11] with Becke's three-parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional (B3LYP)[12] and the 6-31G* basis set.

Figure S1 and S2 illustrate the optimized structures of **2a** and **7**. The angle of C(hydroxylated)–C(cyclobutyl)–C(vinylic) was calculated to be 109.87°. The total energy of **2a** was calculated to be –850.533156 a.u. at the B3LYP/6–31G* level (Figure S1).

The angle of (C(hydroxylated)–C(cyclopropyl)–C(vinylic) was calculated to be 113.73°. The total energy of **7** was calculated to be –811.224077 a.u. at the B3LYP/6–31G* level (Figure S2).

Figure S1. Optimized Structure of **2a**

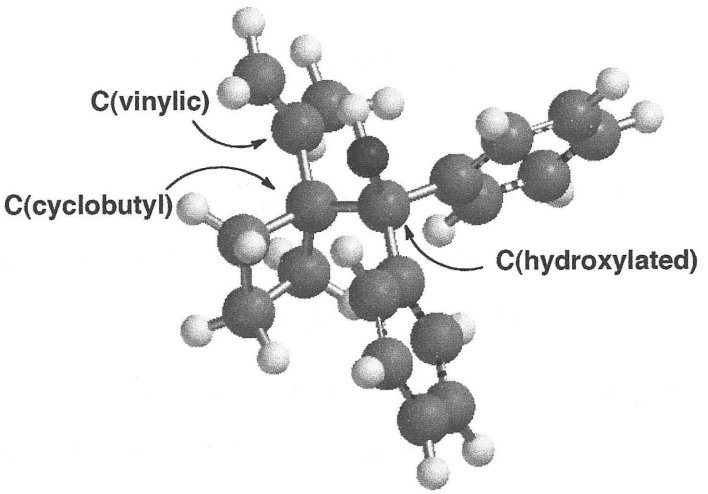


Figure S2. Optimized Structure of **7**

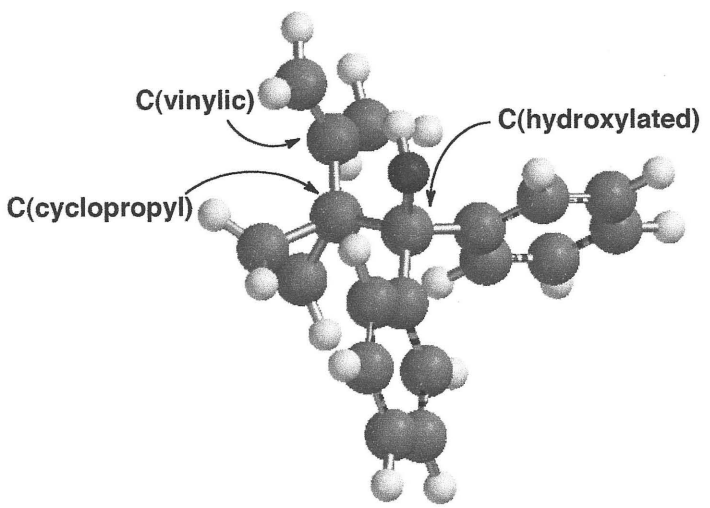


Table S1. The Coordinates of the Atoms in **2a** Optimized at the B3LYP/6–31G* Level

Atom	X	Y	Z
C	–0.072591116	–0.002940375	–0.633952775
C	0.188397365	–1.404339753	0.103354865
C	–0.986818389	–2.409633549	–0.181200400
C	–0.194845417	–1.495758903	1.627936034
C	–1.504100060	–2.236236297	1.265794662
H	–2.384778177	–1.592730147	1.328271857
H	–1.704683870	–3.157590636	1.821571483
H	0.501942176	–2.134092373	2.179197456
H	–0.311700787	–0.563480516	2.184988852
H	–0.609185287	–3.416757273	–0.373430537
H	–1.671758992	–2.137297469	–0.985794133
C	1.571102464	–1.946594933	–0.281711504
C	1.726563280	–2.675286495	–1.400465212
H	2.700071047	–3.060185460	–1.694205235
H	0.890921048	–2.946977450	–2.039836576
C	2.775112460	–1.679698801	0.595708300
H	2.591250930	–1.978314802	1.635008231
H	3.045594647	–0.619948540	0.615861085
H	3.642166489	–2.242937273	0.236991322
O	–0.041625997	–0.280590656	–2.034687989
H	0.809753174	–0.722040718	–2.207191556
C	0.963580334	1.105627336	–0.323989896
C	2.742741251	3.257325717	0.130306180
C	1.517718062	1.332990031	0.944655533
C	1.317026269	1.986776580	–1.356480931
C	2.195878540	3.046933814	–1.135534643
C	2.397840764	2.394359368	1.169044637
H	1.280057592	0.677940763	1.774470859
H	0.889157169	1.831818998	–2.340325248
H	2.450217821	3.711247388	–1.957439978
H	2.814175706	2.540976557	2.162499258
H	3.427056122	4.082864475	0.306096663
C	–1.485173688	0.559894813	–0.366980962
C	–4.085626434	1.558607186	0.098635719
C	–1.780600637	1.299871092	0.787614284
C	–2.514208230	0.356223536	–1.298199379
C	–3.799449058	0.848326313	–1.066617789
C	–3.066806092	1.785663900	1.023467014
H	–0.997844014	1.527542319	1.502688608
H	–2.296962986	–0.177089288	–2.215263586
H	–4.577469096	0.678226526	–1.806485802
H	–3.265586871	2.355109898	1.927754837

Table S2. The Coordinates of the Atoms in **7** Optimized at the B3LYP/6–31G* Level

Atom	X	Y	Z
C	–0.163356972	–0.190864219	–0.559845401
C	0.344570542	–1.414539547	0.288673517
C	–0.034128813	–1.571008285	1.747512783
C	–0.655525769	–2.472571362	0.714093817
H	–0.673709066	–0.821546481	2.204425825
H	0.708547315	–1.993688102	2.420104228
H	–1.704425559	–2.324917804	0.480929733
H	–0.326088854	–3.506075961	0.676931746
C	1.708875354	–1.932554961	–0.140073885
C	1.794486239	–2.868753873	–1.098298581
H	2.754548167	–3.251984762	–1.435954557
H	0.907388726	–3.300419091	–1.553814449
C	2.957359033	–1.382226811	0.509510943
H	3.111516509	–0.326038954	0.264826773
H	3.842138122	–1.942424477	0.189941317
H	2.892080392	–1.443107298	1.603270474
C	–1.640279448	0.150187877	–0.281628214
C	–4.363958169	0.719005378	0.186732285
C	–2.027848864	1.020531537	0.745656614
C	–2.643692096	–0.421345378	–1.078732160
C	–3.989780389	–0.139551466	–0.847637070
C	–3.375822432	1.297721414	0.981684431
H	–1.276597611	1.511691671	1.355049836
H	–2.355357326	–1.077917172	–1.890742604
H	–4.747447225	–0.590786283	–1.483289302
H	–3.648475924	1.978928387	1.783598164
H	–5.412744101	0.940740331	0.365502836
O	–0.123682593	–0.580844612	–1.935861121
H	0.737704763	–1.012378188	–2.077734625
C	0.710202921	1.067862186	–0.363236896
C	2.207093251	3.441402910	–0.074574419
C	1.240975700	1.439011376	0.880637947
C	0.939806272	1.911794568	–1.458357342
C	1.682993297	3.083575115	–1.317208453
C	1.981929557	2.613792414	1.024728580
H	1.088614586	0.801330762	1.744538487
H	0.530155564	1.635963011	–2.423665136
H	1.851031328	3.719768096	–2.182437473
H	2.385682606	2.877217138	1.999016889
H	2.785220964	4.355020916	0.035724465

References and Notes

1. (a) Chen, L.; Shi, M.; Li, C. *Org. Lett.* **2008**, *10*, 5285–5288 and references cited therein. (b) Fujiwara, T.; Iwasaki, N.; Takeda, T. *Chem. Lett.* **1998**, *27*, 741–742 and references cited therein.
2. Histrically important examples. (a) Alder, K.; Ackermann, O. *Chem. Ber.* **1957**, *90*, 1697–1709. (b) Cripps, H. N.; Williams, J. K.; Sharkey, W. H. *J. Am. Chem. Soc.* **1959**, *81*, 2723–2728.
3. Selected examples: (a) Hosomi, A.; Miura, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 835–851. (b) Hojo, M.; Murakami, C.; Nakamura, S.; Hosomi, A. *Chem. Lett.* **1998**, *27*, 331–332. (c) Narasaka, K.; Hayashi, K.; Hayashi, Y. *Tetrahedron* **1994**, *50*, 4529–4542. (d) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402–12403.
4. (a) Wu, Z.; Nguyan, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511. (b) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823–2831.
5. Morlender–Vais, N.; Solodovnikova, N.; Marek, I. *Chem. Commun.* **2000**, 1849–1850.
6. (a) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211. (b) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4463–4469. (c) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2007**, *63*, 5200–5203. (d) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 12650–12651. (e) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2008**, *130*, 5048–5049. (f) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 249–253. (g) Imoto, J.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 393–400.
7. From other groups: (a) Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2005**, 3589–3602. (b) Oh, C. H.; Jung, S. H.; Bang, S. Y.; Park, D. I. *Org. Lett.* **2002**, *4*, 3325–3327.
8. Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545–1548.

9. Optimized at the B3LYP/6–31G* level. For the optimized structures, see Experimental Section.

10. Wiberg, K. B. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312–322.

11. (a) Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, C. D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Voorhis, T.; Oumi, M.; Hirata, S.; Hsu, C.–P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head–Gordon M.; Pople, J. A. *J. Computational Chem.* **2000**, *21*, 1532–1548. (b) Hehre, W. J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations,* Wavefunction, Irvine, 2003.

12. (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100. (b) Lee, C.; Yang W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

Chapter 5

Microwave–Assisted Palladium–Catalyzed Direct Arylation of 1,4–Disubstituted 1,2,3–Triazoles with Aryl Chlorides

Treatment of 1,4–disubstituted 1,2,3–triazoles with aryl chlorides in the presence of potassium carbonate under palladium catalysis and microwave irradiation at 250 °C for 15 min leads to arylation of the triazoles at the 5 position. A variety of functional groups including ester and hydroxy groups are compatible. The procedure is suitable for the regioselective preparation of trisubstituted triazoles. A high temperature, 250 °C , under microwave irradiation accelerates the reaction, allowing for rapid synthesis of trisubstituted triazoles, which are difficult to synthesize selectively.

Introduction

1,2,3–Triazoles are often found in biologically active compounds, and hence important heterocycles in medicinal chemistry as well as organic chemistry. One of the representative methods for the synthesis of 1,2,3–triazoles is the reaction of alkynes with organic azide. Highly regioselective syntheses of 1,4– and 1,5–disubstituted triazoles have been established by using copper[1] and ruthenium[2] catalysts, respectively. However, transition–metal–catalyzed as well as thermal coupling reactions of internal alkynes with organic azides lacks regioselectivity and/or generality.[2,3] Little is known for the regioselective synthesis of 1,4,5–trisubstituted 1,2,3–triazoles. An alternative approach to such trisubstituted triazoles is the use of metalated triazoles. The reaction of magnesium acetylides with organic azides provides 1,5–disubstituted 4–magnesio–1,2,3–triazoles, which further react with various electrophiles.[4] However, this approach has a limitation because of the high reactivity of the magnesium species.

Transition–metal–catalyzed direct arylation reactions of aromatic compounds with aryl halides have attracted increasing attention.[5] Taking advantage of ready availability of 1,4–disubstituted triazoles by the copper–catalyzed reaction,[1] in Chapter 5, the author reports palladium–catalyzed direct arylation of 1,4–disubstituted triazoles with aryl chlorides. The arylation took place at the 5 position, representing a regioselective access to 1,4,5–trisubstituted triazoles. A combined use of tricyclohexylphosphine as the ligand and microwave heating[6] at 250 °C allowed the author to employ aryl chlorides as arylating agents[7] and to complete within only 15 min. Gevorgyan *et al.* independently reported similar arylation reactions[8,9] while the reactions required aryl bromides and a prolonged reaction time of 24 h.

Results and Discussion

A mixture of 1–benzyl–4–phenyl–1,2,3–triazole (**1a**) and *o*–chlorotoluene (**2a**) was heated in a toluene/DMF mixed solvent at 250 °C under microwave irradiation for 15 min in the

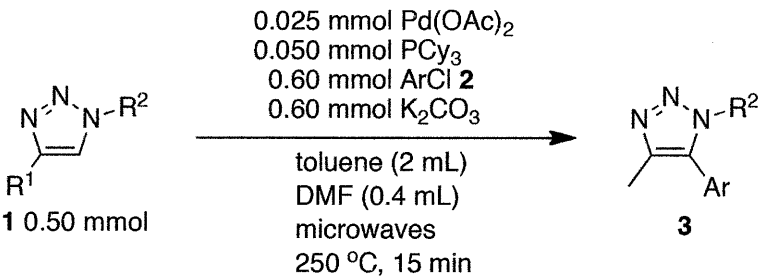
presence of potassium carbonate and a $Pd(OAc)_2/PCy_3$ catalyst. Extractive workup followed by chromatographic purification provided the corresponding arylated product **3aa** in 99% yield (Table 1, entry 1).

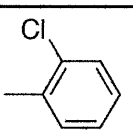
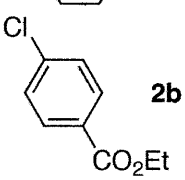
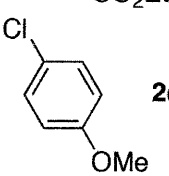
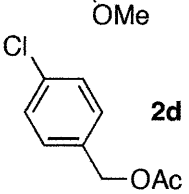
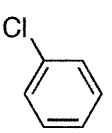
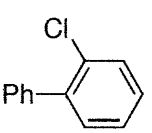
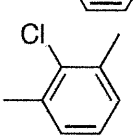
Various combinations of aryl chlorides and triazoles were subjected to the palladium–catalyzed reaction. Aryl chlorides having an electron–withdrawing or –donating group reacted smoothly (entries 2 and 3). Ester functionality was compatible under the reaction conditions (entries 2 and 4). The phenylation reaction of **1a** proceeded in the presence of only 0.5 mol% of $Pd(OAc)_2$ (entry 5). Reducing the amount of the catalyst further led to incomplete conversion (entry 6). Conversions of sterically demanding aryl chlorides **2f** and **2g** were slow, requiring 2 h to proceed to completion (entries 7 and 8).

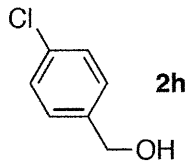
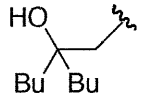
Not only **1a** but also hexyl–substituted **1b** participated in the reaction, albeit with slightly lower efficiency (entries 9–13). The arylation reactions with **2a** and **2b** did not proceed to completion within 15 min, and longer reaction times were necessary (entries 9 and 10). In other cases, larger amounts of potassium carbonate and aryl chlorides were essential to attain high yields (entries 11 and 12). Phenylation of **1b** was less efficient than that of **1a**, requiring 5 mol% of $Pd(OAc)_2$ (entry 13). Unfortunately, the reaction with *p*–chlorobenzyl alcohol (**2h**) resulted in failure to give the expected arylation product and afforded *p*–chlorobenzaldehyde by palladium–catalyzed oxidation reaction (entry 14).[10]

Triazole **1c** having a pyridyl group underwent the phenylation to yield the corresponding trisubstituted triazole in high yield (entry 15). The reaction of **1d** bearing a tertiary alcoholic moiety proceeded smoothly (entry 16) while the presence of a hydroxymethyl group completely retarded the reaction (entry 14). The reaction of 1–aryl–substituted **1e** afforded **3ee** quantitatively (entry 17). The present approach to trisubstituted triazoles allowed for selective preparation of two regioisomers **3ai** and **3fe** (Scheme 1).

Table 1. Pd–Catalyzed Arylation of 1,4–Disubstituted 1,2,3–Triazoles with Aryl Chlorides under Microwave Irradiation

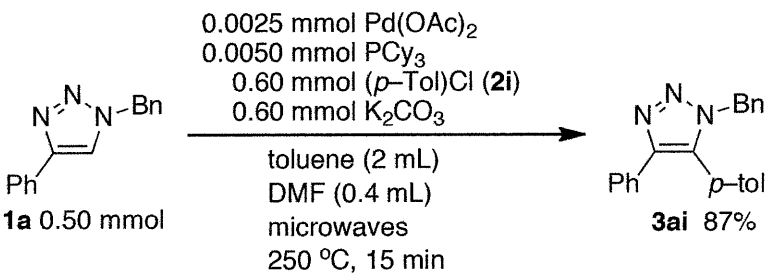


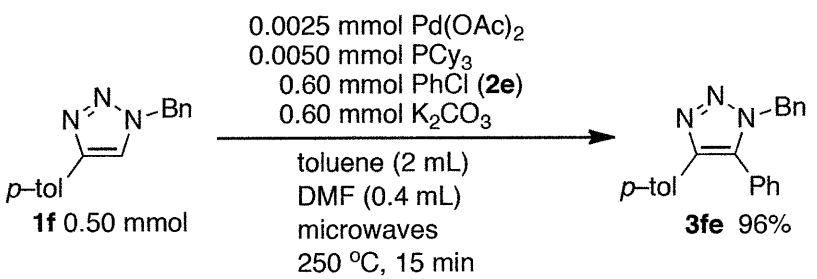
entry	1	R^1	R^2	2	3	yield (%)
1	**1a**	Ph	Bn	 **2a**	**3aa**	99
2	**1a**			 **2b**	**3ab**	84
3	**1a**			 **2c**	**3ac**	90
4	**1a**			 **2d**	**3ad**	77
5[a]	**1a**			 **2e**	**3ae**	98
6[b,c]	**1a**			**2e**	**3ae**	40
7[c,d]	**1a**			 **2f**	**3af**	81
8[c,d]	**1a**			 **2g**	**3ag**	88
9[e]	**1b**	*n*–C_6H_{13}	Bn	**2a**	**3ba**	93
10[f]	**1b**			**2b**	**3bb**	86
11[d]	**1b**			**2c**	**3bc**	90
12[d]	**1b**			**2d**	**3bd**	91
13	**1b**			**2e**	**3be**	88

14	**1b**			 **2h**	**3bh**	–
15	**1c**	4–pyridyl	Bn	**2e**	**3ce**	89
16	**1d**		Bn	**2e**	**3de**	77
17	**1e**	Ph	4–tol	**2e**	**3ee**	100

[a] 0.0025 mmol of $Pd(OAc)_2$ and 0.0050 mmol of PCy_3 were used. [b] 0.00025 mmol of $Pd(OAc)_2$ and 0.00050 mmol of PCy_3 were used. [c] Performed for 2 h. [d] Aryl chloride **2** (1.0 mmol) and K_2CO_3 (1.0 mmol) were used. [e] Performed for 30 min. [f] Performed for 20 min.

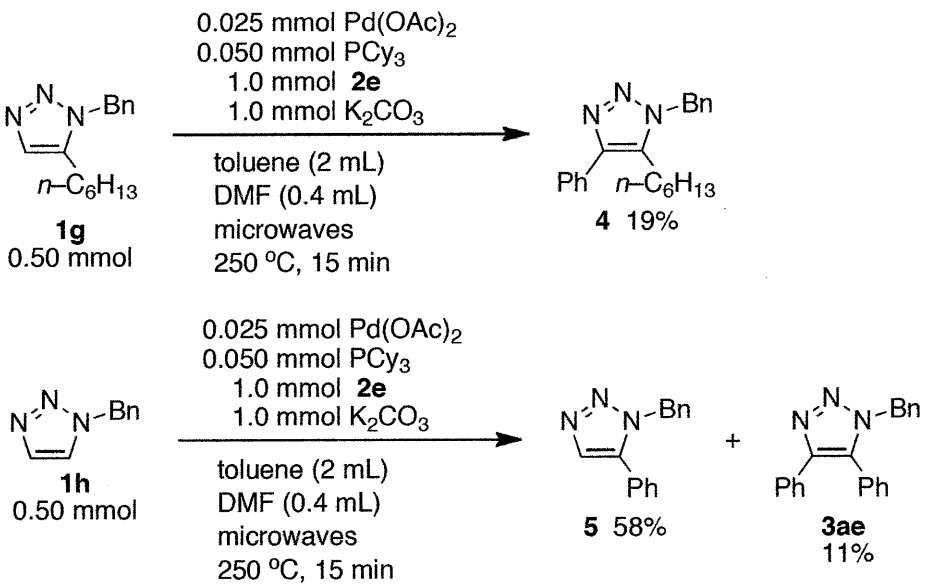
Scheme 1. Regioselective Synthesis of 1,4,5–Trisubstituted 1,2,3–Triazoles





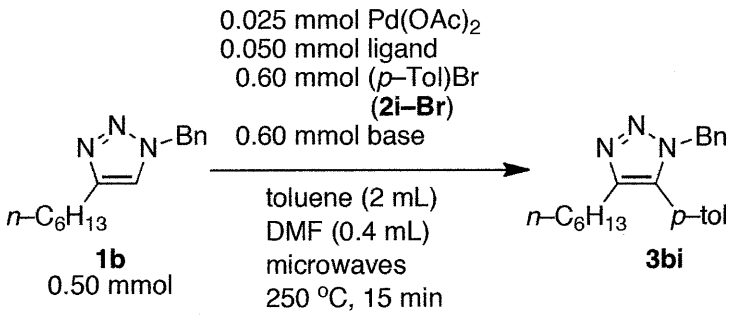
The reaction of 1–benzyl–5–hexyl–1,2,3–triazole (**1g**) was sluggish, providing **4** in only 19% yield (Scheme 2). Monosubstituted 1–benzyl–1,2,3–triazole (**1h**) reacted with chlorobenzene (**2e**) to yield 5–phenyl–substituted product **5** predominantly, along with diphenyl–substituted **3ae**. No 4–phenyl–substituted isomer was detected. The low reactivity of **1g** and the regioselectivity in the reaction of **1h** can be explained based on the plausible mechanism (vide infra).

Scheme 2. Reactions of 1,5–Disubstituted and 1–Monosubstituted 1,2,3–Triazoles



Among ligands screened, PCy_3 proved to be the best ligand (Table 2, entries 1–6). The molar ratio of $Pd(OAc)_2/PCy_3$ had significant influence on yield, and a ratio of 1:2 was best (entries 6–8). The yield heavily depended on the base used. Potassium carbonate and cesium carbonate promoted the reaction, while sodium carbonate was much less effective (entries 6, 9, and 10). Weaker bases such as sodium acetate and triethylamine failed to serve (entries 11 and 12). Palladium acetate was the best precursor, and other palladium salts such as $PdCl_2$, $Pd(OCOCF_3)_2$, $Pd(acac)_2$, $Pd_2(dba)_3$, and $[PdCl(\pi\text{–allyl})]_2$ were much less active or completely inactive.

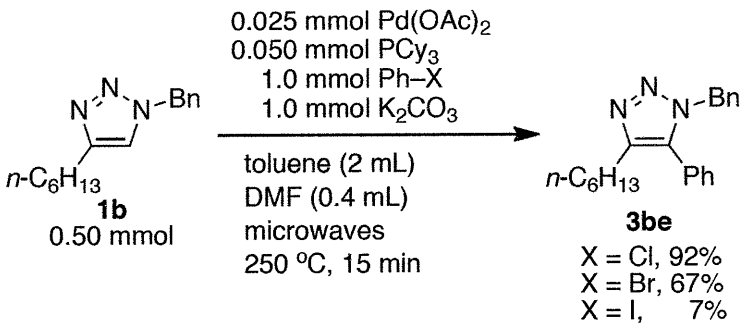
Table 2. Effect of Ligand and Base



entry	ligand	base	yield (%)
1	PPh_3	Cs_2CO_3	56
2	PMe_3	Cs_2CO_3	54
3	P^nBu_3	Cs_2CO_3	28
4	P^tBu_3	Cs_2CO_3	52
5	$P(^cC_5H_9)_3$	Cs_2CO_3	7
6	PCy_3	Cs_2CO_3	64
7	PCy_3 (0.025 mmol)	Cs_2CO_3	12
8	PCy_3 (0.075 mmol)	Cs_2CO_3	44
9	PCy_3	K_2CO_3	77
10	PCy_3	Na_2CO_3	14
11	PCy_3	NaOAc	10
12	PCy_3	Et_3N	7

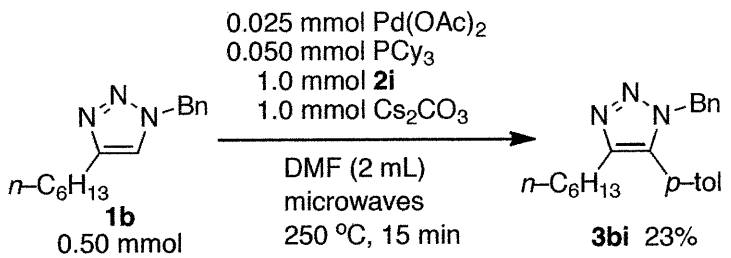
It is worth noting that aryl chloride was superior to aryl bromide and iodide when PCy_3 was used as a ligand (Scheme 3). A slower rate of the oxidative addition of aryl chloride would be suitable to complete the catalytic cycle smoothly (vide infra).

Scheme 3. Direct Arylation Reaction with Various Halobenzenes



The reaction in toluene alone was difficult to perform because microwaves could not heat the reaction mixture up to 250 °C. The reaction in DMF alone afforded the product in very low yield, and most of the starting materials were recovered unchanged (Scheme 4).

Scheme 4. Reaction in DMF



According to the literature,[5,8] a plausible mechanism is shown in Scheme 5. The key step is the reaction of divalent arylpalladium species with triazole (step **B**), which generate a delocalized cationic intermediate **7**. The expanded delocalization would rationalize the facile arylation at the 5 position. The arylation at the 4 position would be unfavorable because of the more localized stabilization of the cationic charge formed (Figure 1).

Scheme 5. Plausible Catalytic Cycle

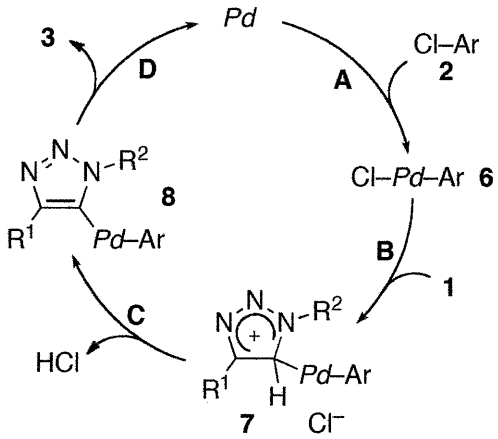
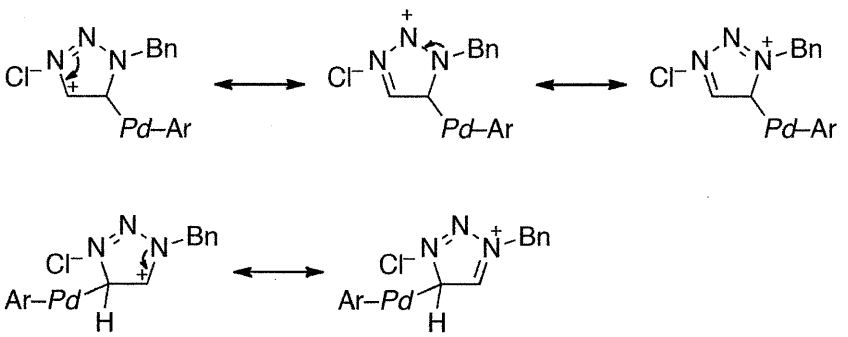


Figure 1. Plausible Cationic Intermediate for Arylation at the 5–Position and 4–Position of Triazoles



Conclusion

The author has developed microwave–assisted palladium–catalyzed direct arylation of 1,4–disubstituted 1,2,3–triazoles with aryl chloride. Copper–catalyzed formal [3+2] cycloaddition reaction of terminal alkynes with organic azides efficiently provides a variety of 1,4–disubstituted 1,2,3–triazoles. The present reaction thus offers concise and rapid synthesis of 1,4,5–trisubstituted 1,2,3–triazoles.

Experimental Section

Instrumentation

Unless otherwise noted, all the reactions were carried out using a focused microwave unit (Biotage Initiator™). The maximum irradiation power is 400 W. Each reaction was run in a 5–mL glass pressure vial, which is a commercially available vial special for the Biotage Initiator™. It took 6 min to reach 250 °C. After reaching the indicated temperatures, controlled microwave irradiation started and continued for 15 min, keeping the reaction temperature constant.

^{1}H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on a Varian UNITY INOVA 500 spectrometer and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.0 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR–8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25–mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Chemicals

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene was stored over slices of sodium. Palladium acetate and tricyclohexylphosphine were obtained from TCI. Tricyclohexylphosphine was diluted to prepare 0.50 M toluene solution and stored under argon. Triazoles **1a–1f** were prepared under copper catalysis according to the literature.[1] Triazole **1g** was prepared by the reported procedure.[4] Triazole **1h** was prepared in 58% yield by treatment of 1,2,3–triazole with benzyl bromide (2 equiv) in the presence of potassium carbonate (2 equiv) in refluxing acetone for 24 h.

Caution: Organic azides can be explosive. Only a small amount of material should be prepared. The author prepared the azide compounds in a 5–mmol scale. They should be handled with care.

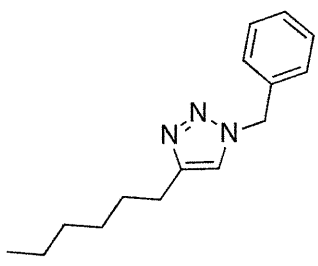
Typical procedure for the arylation reaction (Table 1, entry 2)

Potassium carbonate (83 mg, 0.60 mmol), palladium acetate (5.6 mg, 0.025 mmol), and triazole **1a** (120 mg, 0.50 mmol) were placed in a 5–mL glass pressure vial. The vial was flushed with argon and sealed with a PTFE–silicone septum. Toluene (2.0 mL) and tricyclohexylphosphine (0.50 M in toluene, 0.10 mL, 0.050 mmol) were added, and the mixture was stirred for 1 min. Ethyl *p*–chlorobenzoate (**2b**, 94 mL, 0.60 mmol) and DMF (0.40 mL) were added. The suspension was heated at 250 °C with stirring for 15 min in the microwave reactor. The mixture was then cooled to room temperature. Hydrochloric acid (1 M, 3 mL) was added, and the product was extracted with ethyl acetate (5 mL × 3). The organic layer formed was then washed with brine (5 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated. Purification by silica gel column chromatography (hexane/ethyl acetate = 3:1) provided triazole **3ab** (0.16 g, 0.42 mmol) in 84% isolated yield.

Characterization Data

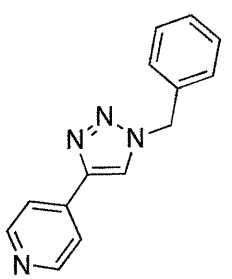
Compounds **1a**,[2] **1e**,[11] **1h**,[12] **3ac**,[13] **3ae**,[2] and **3ee**[14] showed the identical spectra reported in the literature.

1–Benzyl–4–hexyl–1,2,3–triazole (1b)



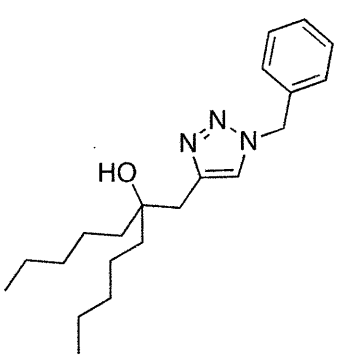
IR (nujol) 1557, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.26–1.36 (m, 6H), 1.63 (quintet, J = 7.5 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 5.49 (s, 2H), 7.17 (s, 1H), 7.23–7.27 (m, 2H), 7.32–7.38 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.21, 22.70, 25.91, 29.08, 29.54, 31.71, 54.13, 120.61, 128.11, 128.75, 129.21, 135.21, 149.18. Found: C, 74.16; H, 8.76%. Calcd for $C_{15}H_{21}N_3$: C, 74.04; H, 8.70%. m.p. 54.9–55.6 °C.

1–Benzyl–4–(4–pyridyl)–1,2,3–triazole (1c)



IR (nujol) 1610, 1563, 1208, 1087, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.60 (s, 2H), 7.32–7.34 (m, 2H), 7.39–7.43 (m, 3H), 7.68 (d, J = 6.0 Hz, 2H), 7.79 (s, 1H), 8.64 (d, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 54.64, 120.10, 121.09, 128.35, 129.23, 129.48, 134.39, 138.04, 145.93, 150.63. Found: C, 71.32; H, 5.08%. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12%. m.p. 127.9–129.1 °C.

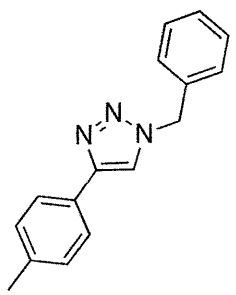
1–Benzyl–4–(2–butyl–2–hydroxyhexyl)–1,2,3–triazole (1d)



IR (nujol) 3372, 3123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 6H), 1.28–1.65 (m, 12H), 2.17 (s, 2H), 2.75 (brs, 1H), 5.51 (s, 2H), 7.22–7.23 (m, 2H), 7.32–7.39 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.06, 23.22, 25.92, 35.30, 39.03, 54.40, 74.09, 124.28 (br), 127.89, 128.64, 129.02,

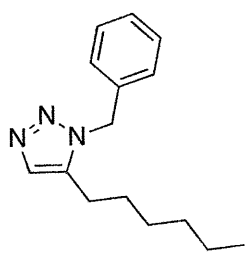
134.85, 146.85(br). Found: C, 72.19; H, 9.09%. Calcd for $C_{19}H_{29}N_3O$: C, 72.34; H, 9.27%. m.p. 69.9–70.1 °C.

1–Benzyl–4–(*p*–tolyl)–1,2,3–triazole (1f)



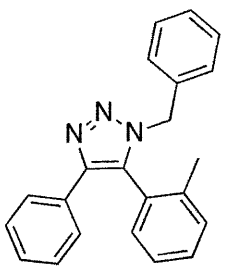
IR (nujol) 1221, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 5.57 (s, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.30–7.32 (m, 2H), 7.37–7.41 (m, 3H), 7.62 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.43, 54.36, 119.29, 125.78, 127.91, 128.23, 128.91, 129.31, 129.64, 134.93, 138.16, 148.49. Found: C, 76.78; H, 5.99%. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06%. m.p. 151.4–152.6 °C.

1–Benzyl–5–hexyl–1,2,3–triazole (1g)



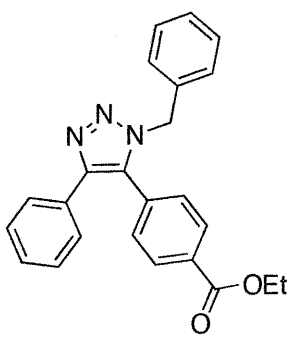
IR (neat) 2931, 1457, 1237 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (t, J = 7.0 Hz, 3H), 1.10–1.22 (m, 6H), 1.44 (quintet, J = 7.5 Hz, 2H), 2.41 (t, J = 7.5 Hz, 2H), 5.43 (s, 2H), 7.07–7.08 (m, 2H), 7.21–7.28 (m, 3H), 7.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.52, 23.22, 27.89, 28.80, 31.42, 51.70, 127.19, 128.34, 129.03, 132.68, 135.19, 137.56. Found: C, 73.80; H, 8.92%. Calcd for $C_{15}H_{21}N_3$: C, 74.04; H, 8.70%.

1–Benzyl–4–phenyl–5–(*o*–tolyl)–1,2,3–triazole (3aa)



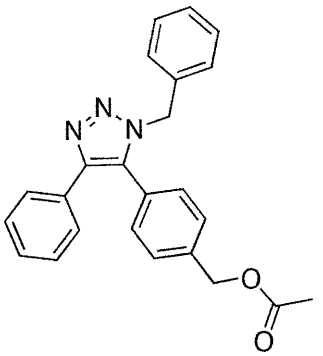
IR (neat) 1457, 1353, 1244, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (s, 3H), 5.27 (d, J = 15.0 Hz, 1H), 5.36 (d, J = 15.0 Hz, 1H), 6.94–6.96 (m, 2H), 7.09–7.11 (m, 1H), 7.18–7.13 (m, 8H), 7.40–7.43 (m, 1H), 7.53–7.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.24, 52.38, 125.86, 126.70, 127.55, 127.82, 128.22, 128.39, 128.70, 128.72, 130.30, 130.49, 130.91, 131.36, 132.99, 134.92, 138.59, 144.59. Found: C, 81.47; H, 5.91%. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.86%.

1–Benzyl–5–(*p*–ethoxycarbonylphenyl)–4–phenyl–1,2,3–triazole (3ab)



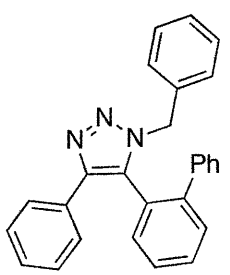
IR (nujol) 1715, 1273 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (t, J = 7.0 Hz, 3H), 4.42 (q, J = 7.0 Hz, 2H), 5.43 (s, 2H), 7.01–7.03 (m, 2H), 7.22–7.26 (m, 8H), 7.51 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.44, 52.37, 61.55, 126.94, 127.50, 128.07, 128.42, 128.66, 128.93, 130.28, 130.35, 130.63, 131.94, 132.56, 133.01, 135.22, 145.07, 165.95. Found: C, 75.35; H, 5.54%. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52%. m.p. 108.8–110.1 °C.

5–{*p*–(Acetoxymethyl)phenyl}–1–benzyl–4–phenyl–1,2,3–triazole (3ad)



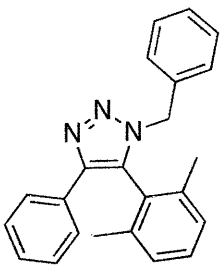
IR (nujol) 1741, 1252 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 5.18 (s, 2H), 5.41 (s, 2H), 7.03–7.05 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.24–7.29 (m, 6H), 7.39 (d, J = 8.0 Hz 2H), 7.54–7.56 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.17, 52.19, 65.68, 126.97, 127.58, 127.84, 127.95, 128.36, 128.65, 128.69, 128.92, 130.48, 131.01, 133.61, 135.54, 137.89, 144.84, 170.92. Found: C, 74.88; H, 5.46%. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52%. m.p. 107.1–108.4 °C.

1–Benzyl–5–(*o*–biphenylyl)–4–phenyl–1,2,3–triazole (3af)



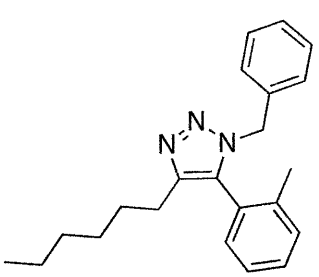
IR (nujol) 1607, 1496, 1354, 1242 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.88 (d, J = 15.0 Hz, 1H), 5.27 (d, J = 15.0 Hz, 1H), 6.89–6.91 (m, 4H), 7.11–7.28 (m, 10H), 7.35 (td, J = 7.0, 2.0 Hz, 1H), 7.54–7.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 52.16, 126.17, 126.47, 127.53, 127.67, 127.96, 128.04, 128.19, 128.41, 128.45, 128.52, 128.63, 130.42, 130.85, 131.14, 131.70, 133.21, 134.83, 139.47, 142.41, 145.31. Found: C, 83.82; H, 5.39%. Calcd for $C_{27}H_{21}N_3$: C, 83.69; H, 5.46%. m.p. 124.9–126.1 °C.

1–Benzyl–5–(2,6–dimethylphenyl)–4–phenyl–1,2,3–triazole (3ag)



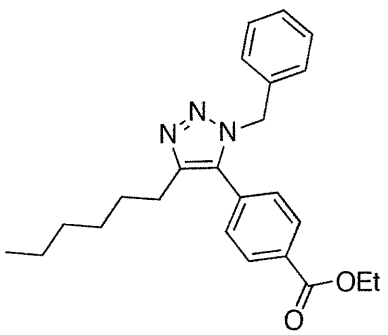
IR (neat) 1608, 1498, 1352, 1243cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 6H), 5.21 (s, 2H), 6.97 (d, J = 7.0 Hz, 2H), 7.12 (d, J = 7.0 Hz, 2H), 7.17–7.25 (m, 6H), 7.34 (t, J = 7.5 Hz, 1H), 7.55 (dt, J = 6.5, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.62, 52.46, 125.30, 126.96, 127.74, 128.17, 128.47, 128.63, 128.67, 128.71, 130.18, 131.28, 131.99, 134.37, 138.45, 144.02. Found: C, 81.22; H, 6.29%. Calcd for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24%.

1–Benzyl–4–hexyl–5–(*o*–tolyl)–1,2,3–triazole (3ba)



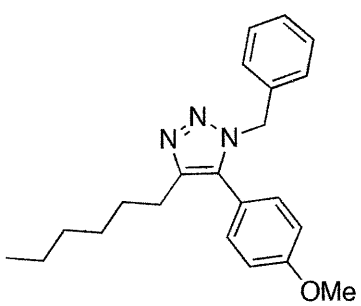
IR (neat) 2928, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.0 Hz, 3H), 1.14–1.31 (m, 6H), 1.56 (quintet, J = 7.5 Hz, 2H), 1.72 (s, 3H), 2.40 (quintet, J = 7.5 Hz, 1H), 2.54 (quintet, J = 7.5 Hz, 1H), 5.22 (d, J = 14.5 Hz, 1H), 5.27 (d, J = 14.5 Hz, 1H), 6.89–6.96 (m, 3H), 7.15–7.23 (m, 5H), 7.34–7.37 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.18, 19.31, 22.70, 25.38, 29.12, 29.24, 31.62, 52.36, 126.15, 127.12, 128.17, 128.22, 128.64, 129.88 130.48, 130.76, 133.57, 135.16, 138.48, 146.55. Found: C, 79.37; H, 8.25%. Calcd for $C_{22}H_{27}N_3$: C, 79.24; H, 8.16%.

1–Benzyl–5–(*p*–ethoxycarbonylphenyl)–4–hexyl–1,2,3–triazole (3bb)



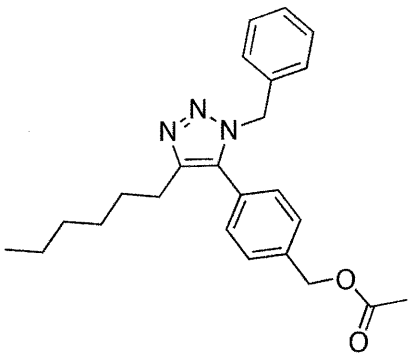
IR (neat) 2930, 1718, 1275, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.0 Hz, 3H), 1.18–1.26 (m, 6H), 1.41 (t, J = 7.0 Hz, 3H), 1.61 (quintet, J = 7.5 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 5.41 (s, 2H), 6.98–7.00 (m, 2H), 7.19 (d, J = 7.5 Hz, 2H), 7.23–7.25 (m, 3H), 8.07 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.17, 14.49, 22.67, 25.26, 29.11, 29.68, 31.60, 52.34, 61.53, 127.43, 128.33, 128.93, 129.81, 130.12, 131.33, 132.37, 133.56, 135.57, 146.70, 166.05. Found: C, 73.58; H, 7.44%. Calcd for $C_{24}H_{29}N_3O_2$: C, 73.63; H, 7.47%.

1–Benzyl–4–hexyl–5–(*p*–methoxyphenyl)–1,2,3–triazole (3bc)



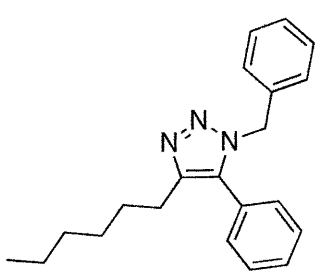
IR (neat) 2930, 1507, 1252 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.0 Hz, 3H) 1.16–1.29 (m, 6H), 1.62 (quintet, J = 7.5 Hz, 2H), 2.59 (t, J = 7.5 Hz, 2H), 3.84 (s, 3H), 5.37 (s, 2H), 6.91–6.93 (m, 2H), 7.00–7.03 (m, 4H), 7.23–7.26 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.19, 22.69, 25.28, 29.12, 29.74, 31.64, 51.95, 55.49, 114.44, 119.69, 127.46, 128.09, 128.80, 131.17, 134.33, 136.02, 146.22, 160.36. Found: C, 75.84; H, 7.81%. Calcd for $C_{22}H_{27}N_3O$: C, 75.61; H, 7.79%.

5–{*p*–(Acetoxymethyl)phenyl}–1–benzyl–4–hexyl–1,2,3–triazole (3bd)



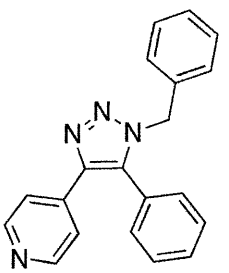
IR (neat) 2930, 1744, 1227, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.0 Hz, 3H), 1.16–1.31 (m, 6H), 1.62 (quintet, J = 7.5 Hz, 2H), 2.14 (s, 3H), 2.59 (t, J = 7.5 Hz, 2H), 5.15 (s, 2H), 5.39 (s, 2H), 6.99–7.01 (m, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.24–7.25 (m, 3H), 7.39 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.18, 21.13, 22.67, 25.22, 29.10, 29.73, 31.62, 52.06, 65.73, 127.39, 127.63, 128.17, 128.53, 128.84, 130.04, 134.05, 135,84, 137.32, 146.37, 170.91. Found: C, 73.35; H, 7.52%. Calcd for $C_{24}H_{29}N_3O_2$: C, 73.63; H, 7.47%.

1–Benzyl–4–hexyl–5–phenyl–1,2,3–triazole (3be)



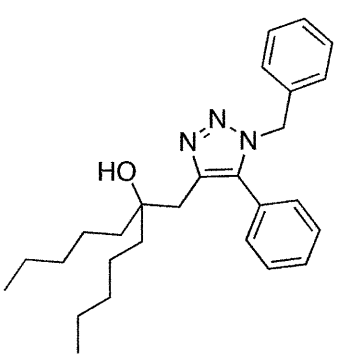
IR (neat) 2929, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.0 Hz, 3H), 1.16–1.28 (m, 6H), 1.62 (quintet, J = 8.0 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H), 5.40 (s, 2H), 6.98–7.01 (m, 2H), 7.10–7.12 (m, 2H), 7.22–7.25 (m, 3H), 7.38–7.44 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.17, 22.66, 25.22, 29.08, 29.71, 31.60, 52.08, 127.48, 127.79, 128.12, 128.78, 128.97, 129.33, 129.84, 134.49, 135.85, 146.27. Found: C, 79.02; H, 7.93%. Calcd for $C_{21}H_{25}N_3$: C, 78.96; H, 7.89%.

1–Benzyl–5–phenyl–4–(4–pyridyl)–1,2,3–triazole (3ce)



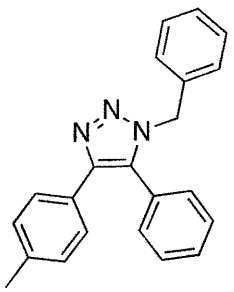
IR (nujol) 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.41 (s, 2H), 7.01–7.03 (m, 2H), 7.14–7.16 (m, 2H), 7.24–7.28 (m, 3H), 7.41–7.47 (m, 4H), 7.53–7.56 (m, 1H), 8.48 (d, J = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 52.35, 120.72, 127.19, 127.75, 128.54, 128.97, 129.65, 130.02, 130.46, 135.09, 138.82, 138.79, 142.09, 150.09. Found: C, 76.79; H, 5.20%. Calcd for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16%. m.p. 155.4–156.7 °C.

1–Benzyl–4–(2–butyl–2–hydroxyhexyl)–5–phenyl–1,2,3–triazole (3de)



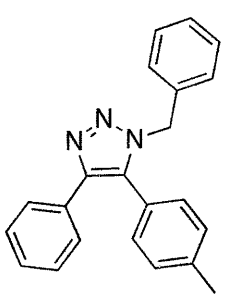
IR (neat) 3448, 2955, 1456, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 6H), 1.04–1.43 (m, 12H), 2.73 (s, 2H), 3.82 (s, 1H), 5.43 (s, 2H), 6.97–7.00 (m, 2H), 7.09–7.11 (m, 2H), 7.22–7.26 (m, 3H), 7.40–7.47 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.21, 23.44, 26.07, 34.20, 38.94, 52.29, 74.54, 127.26, 127.45, 128.31, 128.90, 129.15, 129.66, 129.88, 135.63, 135.99, 143.35. HRMS (FAB), Found: 391.2617. Calcd for $C_{25}H_{33}N_3O$: 391.2624.

1–Benzyl–5–phenyl–4–(*p*–tolyl)–1,2,3–triazole (3fe)



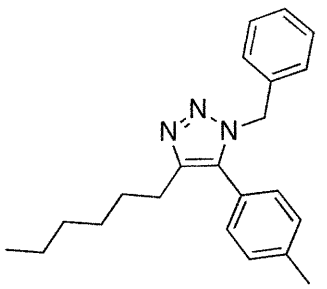
IR (nujol) 1256, 1156, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 5.41 (s, 2H), 7.02–7.04 (m, 2H), 7.06–7.08 (m, 2H), 7.13–7.16 (m, 2H), 7.24–7.27 (m, 3H), 7.39–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.36, 52.16, 126.78, 127.64, 128.14, 128.20, 128.25, 128.83, 129.27, 129.29, 129.74, 130.27, 133.69, 135.58, 137.62, 144.78. Found: C, 80.97; H, 5.90%. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.86%. m.p. 125.8–127.0 °C.

1–Benzyl–4–phenyl–5–(*p*–tolyl)–1,2,3–triazole (3ai)



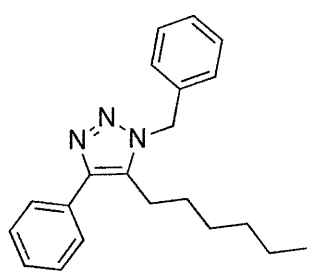
IR (nujol) 1366, 1313, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 5.40 (s, 2H), 7.04–7.08 (m, 4H), 7.21–7.28 (m, 8H), 7.60–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.49, 51.89, 124.73, 126.71, 127.50, 127.64, 128.12, 128.44, 128.71, 129.94, 129.96, 131.14, 134.06, 135.58, 139.79, 144.41. Found: C, 80.93; H, 5.94%. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.86%. m.p. 113.2–114.9 °C.

1–Benzyl–4–hexyl–5–(*p*–tolyl)–1,2,3–triazole (3bi)



IR (neat) 2927, 1455cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.0 Hz, 3H), 1.17–1.29 (m, 6H), 1.62 (quintet, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 2.60 (t, J = 7.5 Hz, 2H), 5.38 (s, 2H), 6.99–7.02 (m, 4H), 7.20–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.98, 21.31, 22.50, 25.08, 28.93, 29.55, 31.45, 51.78, 124.55, 127.29, 127.90, 128.60, 129.50, 129.55, 134.38, 135.84, 139.18, 146.00. Found: C, 78.99; H, 8.14%. Calcd for $C_{22}H_{27}N_3$: C, 79.24; H, 8.16%

1–Benzyl–5–hexyl–4–phenyl–1,2,3–triazole (4)



IR (neat) 2930, 1497, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, *J* = 7.0 Hz, 3H), 1.12–1.26 (m, 6H), 1.35 (quintet, *J* = 8.0 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 5.56 (s, 2H), 7.21 (d, *J* = 7.0 Hz, 2H), 7.32–7.37 (m, 4H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.57, 23.40, 28.53, 29.22, 31.34, 52.24, 127.18, 127.27, 127.81, 128.48, 128.82, 129.14, 131.95, 133.85, 135.48, 144.91. Found: C, 79.02; H, 7.93%. Calcd for $C_{21}H_{25}N_3$: C, 78.96; H, 7.89%.

References and Notes

1. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599 (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
2. Zhang, L.; Chen, X.; Xue, P.; Y. Sun, H. H.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.
3. (a) Díez–González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558–7564. (b) Majireck, M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680–8683 and references cited therein.
4. Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237–1240.
5. (a) Dyker, G. Ed. *Handbook of C–H Transformations*; Wiley–VCH: Weinheim, Germany, 2005. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (d) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (e) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (g) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, 36, 1173–1193.
6. Reviews for microwave–assisted organic reactions: (a) *Microwave Assisted Organic Synthesis*, Tierney, J. P.; Lidström, P. Eds., Blackwell Publishing: Victoria, 2005. (b) *Microwave Methods in Organic Synthesis*, Larhed, M.; Olofsson, K. Springer–Verlag: Berlin, 2006. (c) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661. (d) Tokuyama, H. Nakamura, M. *J. Synth. Org. Chem., Jpn.* **2005**, *63*, 523–538. (e) de la Hoz, A.; Diaz–Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178. (f) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284. (g) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283. (h) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432. (i) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1–47.
7. Examples of the use of aryl chlorides in direct arylation of heterocycles: (a) Akita, Y.; Inoue,

A.; Yamamoto, K.; Ohta, A.; Kurihara, T.; Shimizu, M. *Heterocycles* **1985**, *23*, 2327–2333. (b) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981–3983.

8. Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333–2336.
9. Palladium–catalyzed direct arylation of 1,2,4–triazole with aryl chloride was reported: Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449–1451.
10. (a) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755. (b) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185–3189. (c) Muzart, J. *Tetrahedron* **2003**, *59*, 5789–5816.
11. Zhao, Y.–B.; Yan, Z.–Y.; Liang, Y.–M. *Tetrahedron Lett.* **2006**, *47*, 1545–1549.
12. Holzer, W. *Tetrahedron* **1991**, *47*, 9783–9792.
13. Deng, J.; Wu, Y.–M.; Chen, Q.–Y. *Synthesis* **2005**, 2730–2738.
14. Wang, Z.–X.; Qin, H.–L. *Chem. Commun.* **2003**, 2450–2451.

Publication List

I. Parts of the present thesis have been published in the following journals.

Chapter 1 $Pd(OAc)_2/P(^cC_6H_{11})_3$–Catalyzed Allylation of Aryl Halides with Homoallyl Alcohols via Retro–Allylation
Masayuki Iwasaki, Sayuri Hayashi, Koji Hirano, Hideki Yorimitsu, and Koichiro Oshima
J. Am. Chem. Soc. **2007**, *129*, 4463–4469.

Chapter 2 Microwave–Assisted Palladium–Catalyzed Allylation of Aryl Halides with Homoallyl Alcohols via Retro–Allylation
Masayuki Iwasaki, Sayuri Hayashi, Koji Hirano, Hideki Yorimitsu, and Koichiro Oshima
Tetrahedron **2007**, *63*, 5200–5203.

Chapter 3 Synthesis of Prenylarenes and Related (Multisubstituted Allyl)arenes from Aryl Halides and Homoallyl Alcohols via Palladium–Catalyzed Retro–Allylation
Masayuki Iwasaki, Hideki Yorimitsu, and Koichiro Oshima
Bull. Chem. Soc. Jpn. **2009**, *82*, 249–253.

Chapter 4 Synthesis of (2–Arylethylidene)cyclobutanes by Palladium–Catalyzed Reaction of Aryl Halides with Homoallyl Alcohols Bearing a Trimethylene Group at the Allylic Position
Masayuki Iwasaki, Hideki Yorimitsu, and Koichiro Oshima
Synlett, **2009** 2177–2179.

Chapter 5 Microwave–Assisted Palladium–Catalyzed Direct Arylation of 1,4–Disubstituted 1,2,3–Triazoles with Aryl Chlorides
Masayuki Iwasaki, Hideki Yorimitsu, and Koichiro Oshima
Chem. Asian J. **2007**, *2*, 1430–1435.

II. Other Publications not included in this thesis.

(1) Pentamethylcyclopentadienide in Organic Synthesis: Nucleophilic Addition of Lithium Pentamethylcyclopentadienide to Carbonyl Compounds and Carbon–Carbon Bond Cleavage of the Adducts Yielding the Parent Carbonyl Compounds

Minoru, Uemura, Kazunari Yagi, Masayuki Iwasaki, Kenichi Nomura, Hideki Yorimitsu, and Koichiro Oshima

Tetrahedron **2006**, *62*, 3523–3535.

(2) Synthesis of β, γ–Unsaturated Ketones by Allylation of Pentamethylcyclopentadienyl Ketones Followed by Removal of Pentamethylcyclopentadiene

Masayuki Iwasaki, Eiji Morita, Minoru Uemura, Hideki Yorimitsu, and Koichiro Oshima

Synlett **2007**, 167–169.

(3) Synthesis of β, γ–Unsaturated Ketones from Acid Chlorides through Carbon–Pentamethylcyclopentadienyl Bond Formation and Cleavage

Minoru Uemura, Masayuki Iwasaki, Eiji Morita, Hideki Yorimitsu, and Koichiro Oshima

Bull. Chem. Soc. Jpn. **2007**, *80*, 2400–2405.

(4) Palladium–Catalyzed Mizoroki–Heck Reactions of 2–Methylene–1,3–dithiane 1–Oxide with Aryl Iodides

Eiji Morita, Masayuki Iwasaki, Suguru Yoshida, Hideki Yorimitsu, and Koichiro Oshima

Chem. Lett. **2009**, *38*, 624–625.

(5) Copper–Catalyzed Arylation of Chlorosilanes with Grignard Reagents

Eiji Morita, Kei Murakami, Masayuki Iwasaki, Hideki Yorimitsu, and Koichiro Oshima

Bull. Chem. Soc. Jpn. **2009**, *82*, 1012–1014.

(6) Palladium–Catalyzed Addition of Silyl–Substituted Chloroalkynes to Terminal Alkynes
Tatsuya Wada, Masayuki Iwasaki, Azusa Kondoh, Hideki Yorimitsu, and Koichiro Oshima
Chem. Eur. J. **2010**, *16*, 10671–10674.

Acknowledgment

The studies described in this thesis have been carried out under the direction of Professor Koichiro Oshima at Kyoto University from April, 2005 to November, 2010.

The author wishes to express his grateful acknowledgment to Professor Koichiro Oshima for his invaluable guidance, constant encouragement, and fruitful discussion throughout the course of this work. He is deeply grateful to Associate Professor Hideki Yorimitsu for his practical guidance, helpful discussions, and considerate suggestions.

The author wishes to show his gratitude to Professor Tamejiro Hiyama, Professor Seijiro Matsubara, Professor Kazuo Akagi and Professor Koji Otsuka for their helpful suggestions. He is thankful to Associate Professor Masaki Shimizu, Dr. Yoshiaki Nakao, and Dr. Takuya Kurahashi for their generous help.

He is also thankful to Oshima group's secretary, Ms. Mika Ogishi for her various supports. It is great pleasure to express his appreciation to all the members of Oshima group for their active and helpful discussions.

The author wishes to express his gratitude to Professor Valery V. Fokin for his guidance at The Scripps Research Institute from April, 2009 to March, 2010. He is also grateful to all the members of Sharpless–Fokin group for kind assistance during his stay at La Jolla.

The author would like to express his appreciation to Professor Atsuhiro Osuka for his utmost guidance at Graduate School of Science, Kyoto University. He also wishes to thank Dr. Naoki Aratani and all the members in Osuka group for their friendship.

Financial support from JSPS, Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists, was indispensable, and the author sincerely appreciates the support.

Finally, the author would like to express his sincere appreciation to his wife, Megumi Iwasaki, and his parents , Yutaka and Shizuko Iwasaki for their encouragement and continuous assistance.

Masayuki Iwasaki